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ORAL PENICILLIN FOR CHILDREN WITH RHEUMATIC FEVER

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THIS study was undertaken to determine whether oral penicillin under the conditions described in this report is effective in the prevention of Lancefield Group A hemolytic streptococcal upper respiratory infections and in the elimination of throat carriers in children. The majority of the patients were actively and chronically ill with rheumatic fever and rheumatic heart disease.

Early studies[1, 2] indicated that oral penicillin in doses similar to those employed in parenteral injections yielded inadequate blood plasma levels with small amounts excreted in the urine. Gastric acidity and reduced pH were considered to be responsible factors for its destruction. Therefore, many preparations of penicillin with antacids, buffers, capsules, oils, and waxes were introduced and studied.

When 100,000 units of penicillin were given on a fasting stomach[3] the urinary excretion level was of the same order of magnitude or larger than the urinary excretion level following parenteral injections of 20,000 units. Gastric acidity[4] is probably not a major factor in the destruction of orally administered penicillin. However, it is generally agreed that food in the stomach and active gastric digestion markedly reduces the effective absorption of this antibiotic.[5]

The efficacy of orally administered penicillin in the treatment of acute infections produced by penicillin-susceptible organisms is now established. Many authors[6-10] agree that if oral doses of 100,000 units given every three hours are employed for adults, effective plasma penicillin levels can be achieved comparable with those obtained with intramuscular injections of 20,000 units every three hours. Hoffman and associates[11] administered crystalline potassium penicillin in the treatment of acute respiratory infections in children. Their results indicate that a satisfactory therapeutic plasma penicillin concentration can be maintained when 3,000 units per kilogram are administered every three hours.

Numerous medical authorities have noted the relationship of the Lancefield group A hemolytic streptococcus in the genesis of rheumatic fever. Coburn[12] and others have directed attention to this pathogen as the agent capable, at times, of inciting rheumatic fever. The evidence favoring Coburn's observations prompted Paul[13] to suggest that rheumatic fever be considered one of the special or peculiar manifestations of a hemolytic streptococcal infection.

From the LaRabida Jackson Park Sanitarium, Chicago.

Abundant evidence favoring an undefined relationship between the hemolytic streptococcus and rheumatic fever is now available. The portal of entry is generally assumed to be the upper respiratory tract.[14] Numerous recorded observations indicate that upper respiratory tract infections caused by a Lancefield Group A hemolytic streptococcus may initiate a train of reactions in the host resulting in a clinical state and specific lesions characteristic of the disease. The seasonal occurrence of rheumatic fever at the time of year when hemolytic streptococcal infections are prevalent, the association of epidemics of rheumatic fever following certain epidemics of hemolytic streptococcal upper respiratory infection, the appearance of definite immune responses in rheumatic fever which are characteristic of invasion of the tissues by hemolytic streptococci, and the reduction of the incidence of recurrent attacks through the prophylactic use of the sulfonamides[15] lends further support to the view that these organisms are etiologic factors in the pathogenesis of rheumatic fever.

PLAN OF STUDY

Oral penicillin, crystalline G* was administered over a seven-month period to sixty-three hospitalized children (census 45-50). Their ages ranged from 4 to 13 years, the average being 8.7 years. Most of these were chronically ill with varying degrees of active rheumatic fever or active rheumatic carditis. Each child received 200,000 units of penicillin daily in equally divided doses. One hundred thousand units were given one-half hour before breakfast and 100,000 units were given one-half hour before supper. The penicillin tablets were buffered with calcium carbonate and, in most cases, variously flavored and sweetened to improve their palatability. These were consumed like candy.

Initially one-half of the patient census was chosen for penicillin prophylaxis by blindfold selection; thereafter, alternate admissions were given oral penicillin. An equivalent group served as controls and these were given placebos appearing and tasting like the flavored and buffered medication. The control patients were equally distributed among those receiving penicillin to challenge the efficacy of penicillin prophylaxis. Their age range was from 4 to 13 years with an average of 8.9 years.

METHOD

Admission throat and gingival swabs were cultured on a solid medium containing Bacto blood agar base (Difco) plus 5 per cent defibrinated sheep's blood. These plates were incubated aerobically at 37° C. for twenty to twenty-four hours. The above procedure was repeated on all patients and throat cultures on all personnel were conducted at weekly intervals and specifically as requested by members of the medical attending staff. Such specific requests were dependent upon the clinical symptoms or findings suggesting the presence of an upper respiratory infection of streptococcal origin.

Positive blood agar cultures were classified from 1 plus to 4 plus according to the number of hemolytic streptococcal colonies appearing on the medium. Definite and suspicious beta hemolytic strains were isolated and inoculated onto a

*The penicillin tablets used in this study were buffered with calcium carbonate, some unflavored and some flavored (Confets). These were generously supplied by the Schenley Laboratories, Inc., N. Y.

second blood agar medium and incubated for eighteen to twenty hours. Colonies producing beta hemolysis were examined microscopically. An inoculum of a confirmed beta hemolytic streptococcal colony was transferred to a large centrifuge tube containing 40 ml. sterile tryptose phosphate broth (Difco) plus 1 per cent sterile horse serum (Lederle) and incubated for eighteen hours. The centrifuged sediment was digested and an extract was prepared according to the method of Lancefield.[16] Small bore glass tubing with an outer diameter of 4 mm. was cut into 3.5 to 4 cm. lengths and one end was sealed. Into such tubes lined erect in plasticine spread on a wooden block a small amount of prepared extract was layered over Lancefield Group A antistreptococcal serum (Lederle). A positive precipitin reaction was indicated by the formation of a definite, cloudy, white ring at the junction of the extract and the serum. These tubes were incubated for thirty minutes and re-examined.

Samples of blood for the determination of penicillin levels were drawn routinely one hour and three hours after the ingestion of the antibiotic. Estimation of plasma penicillin levels was conducted with the Rammelkamp[17] serial dilution method employing C 203 strain of Group A hemolytic streptococcus as the test organism. Furthermore, the Welch[11, 18] serial dilution method employing *Bacillus subtilis* (NRRL B-558) as the organism of standard sensitivity was also utilized. The latter is prepared from stock agar slants by incubation on a shaking machine at 30° C. for eighteen to twenty hours. Serial dilutions of a standard penicillin solution (1 unit per milliliter in sterile physiologic saline) usually produces 6 tubes with no growth. Thus an unknown plasma similarly diluted and also producing 6 clear tubes contains one unit per milliliter. The lower limit of penicillin concentration that can be detected in such a standard is 0.03 unit per milliliter. Occasionally the standard may show 7 clear tubes which allows measurement to 0.015 unit per milliliter.

To insure greater accuracy of measurement, three standard series were prepared for each day of bioassays. The results were discarded if the standards did not give consistent measurements. Blood was drawn for penicillin levels under aseptic conditions and transferred to tubes containing 0.02 Gm. sodium citrate. The plasma was separated and used for the analysis. In previously reported studies[7, 8, 11] specific inhibitors to the growth of *Bacillus subtilis* in plasma of normal subjects could not be detected.

Penicillin-sensitivity tests were conducted upon fifty-seven strains of confirmed Group A hemolytic streptococci. Two techniques were employed. The first was a serial dilution method controlled with a stock strain of hemolytic streptococcus, C203, the sensitivity of which remained practically constant at 0.008 unit per milliliter. Penicillin G was diluted serially in brain-heart infusion broth (Difco) in concentrations varying from 1.0 units per milliliter to 0.002 unit per milliliter. To each prepared series of dilutions was added 0.1 ml. of a 1-100 dilutions of an eighteen-hour broth culture of the organism to be tested. These were incubated at 37° C. for eighteen to twenty-four hours. The last clear tube of each series containing the least amount of penicillin which inhibits bacterial growth is regarded as indicating the penicillin sensitivity of the organism. The second technique employed the Fleming[19] ditch plate method.

RESULTS

A. Classification of Patients.—Children aged 4 to 13 years afflicted with or suspected of having active rheumatic fever and/or active rheumatic heart disease were referred by private physicians and hospital clinics for management. Approximately 50 per cent were admitted directly from the home and these were segregated for one week. The diagnostic criteria of Jones[20] were employed to establish the clinical diagnosis, while the laboratory and clinical criteria of Taran[21] were used to establish that the diagnosed rheumatic disease was clinically active or inactive. The term "rheumatic state" signifies rheumatic fever and/or rheumatic carditis. A clinical classification of the 127 patients follows in Table I.

TABLE I. CLINICAL CLASSIFICATION OF PATIENTS

	PENICILLIN TREATED	PLACEBO TREATED
Active rheumatic state	33	39
Inactive rheumatic state	7	7
Possible rheumatic fever	13	5
Nonrheumatic	10	13
Total	63	64

B. Results of Penicillin Prophylaxis.—Sixty-three patients received oral penicillin, 200,000 units daily in equally divided doses, over a seven-month period which represented 4,239 days of penicillin therapy. Sixty-four patients received placebos during the identical seven-month period which represented 4,573 days.

No upper respiratory infections appeared in the treated group of patients from whom a confirmed Group A hemolytic streptococcus was isolated in throat cultures. From one patient during the last week of the study a single beta hemolytic colony was identified as a member of Lancefield Group A (it did not possess increased penicillin resistance as indicated by its inability to grow in the presence of 0.008 units of penicillin G per milliliter). Thus, from a total of 630 throat cultures on sixty-three patients, a single, confirmed group A beta hemolytic streptococcal colony was isolated in only one instance. This represents one throat carrier among the treated group.

Four sporadic confirmed Group A hemolytic streptococcal upper respiratory infections (pharyngitis and/or tonsillitis) appeared among the sixty-four children receiving placebos. Identified Group A* hemolytic streptococci were recovered in the throat cultures of eleven additional patients, of whom five were admission throat carriers. Thus four active upper respiratory infections and eleven carriers of these organisms were identified among the sixty-four children. Positive isolations of Group A hemolytic streptococci were obtained in fifty-seven throat cultures from a total of 677 attempts in this untreated group.

Four patients on admission (one revealing active clinical pharyngitis and tonsillitis) whose throat cultures revealed the confirmed presence of Group A hemolytic streptococci were given prophylactic oral penicillin. Their throat cultures became negative (average 3 to 4 days) and remained so throughout the study period.

*Further serologic classification of these group A beta hemolytic streptococci into specific types was not possible because the necessary type-specific serum was unavailable.

A four-month study of gingival cultures was undertaken. No confirmed group A beta hemolytic streptococci were recovered from the gingivae.

C. Penicillin Sensitivity Studies.—Penicillin sensitivity determinations were conducted on the fifty-seven strains of Group A hemolytic streptococci isolated during the period of the study. It is evident from Table II that the majority of these strains are sensitive to 0.008 unit per milliliter penicillin G when the serial dilution method is employed. This corresponds to the penicillin sensitivity of the standard C 203 strain obtained in the majority of the titrations.

While not all the isolated strains have been completely studied by the Fleming technique, none possess greater penicillin resistance than shown in Table II.

No general increase in penicillin resistance was observed during the course of this brief study.

TABLE II. PENICILLIN SENSITIVITY OF FIFTY-SEVEN STRAINS OF GROUP A HEMOLYTIC STREPTOCOCCI

PENICILLIN SENSITIVITY (UNIT PER ML.)	NUMBER OF STRAINS
.004	4
.008	32
.015	12
.03	4

D. Comparison of the Results of the Rammelkamp and Welch Serial Dilution Methods for the Bioassay of Plasma Penicillin.—Table III shows the results of two successive blood plasma bioassays for penicillin, each conducted upon the same plasma specimen of six older children of varying age and weight. The blood was drawn one hour and three hours after the morning ingestion of 100,000 units of penicillin. It is evident from the results that a single dose of 100,000 units of buffered penicillin in a fasting state promotes a satisfactory therapeutic blood plasma penicillin level. In most instances the penicillin level remained within the therapeutic range for three hours after its ingestion.

TABLE III. COMPARISON OF THE RAMMELKAMP AND WELCH PENICILLIN BIOASSAY PROCEDURES

			1 HOUR		3 HOURS	
PATIENT	AGE	WEIGHT (KG.)	RAMMELKAMP (UNITS PER ML.)	WELCH (UNITS PER ML.)	RAMMELKAMP (UNITS PER ML.)	WELCH (UNITS PER ML.)
S.W.	9	22.7	0.5	0.25	0.03	0.06
J.H.	13	35.0	0.125	0.125	0.03	0.06
R.H.	8	21.6	0.25	0.25	0.06	0.06
R.C.	10	34.8	0.125	0.125	0.06	0.06
M.T.	10	27.4	0.125	0.25	0.03	0.06
G.B.	9	44.8	0.06	0.06	0.015	<0.03
C.K.	8	26.1	0.25	0.25	0.06	0.03
R.H.	12	46.0	0.06	0.06	<0.015	0.03
N.M.	9	25.1	0.125	0.125	0.03	0.03
W.R.	9	29.8	0.125	0.125	0.03	0.03
J.P.	10	28.5	0.125	0.125	0.015	<0.03
A.K.	10	42.5	0.06	0.03	<0.015	<0.03

The results of these and other penicillin bioassays employing both techniques on identical blood samples indicated either method satisfactory for routine plasma penicillin bioassays. Because the Welch serial dilution method appeared most suitable for routine bioassays, it was selected and employed during the latter part of the study and the Rammelkamp serial dilution method was discontinued.

DISCUSSION

For many years physicians have attempted to lessen the frequency of rheumatic recurrences by the prophylactic use of various drugs. The early studies employed salicylates between rheumatic attacks and later they were given coincident with and for about a month following an upper respiratory infection in rheumatic children.[22] The salicylates, however, do not prevent recurrences by a direct chemotherapeutic effect on the hemolytic streptococcus.

The efficacy of the sulfonamides in the treatment of infections resulting from invasion of the tissues by the group A hemolytic streptococcus stimulated numerous studies in which small doses of sulfonamides were employed in the prevention of rheumatic recurrences in susceptible children. Results of sulfonamide prophylaxis as employed in civilian populations have been reviewed.[15] These indicate that the drug markedly decreases the rheumatic recurrence rate.

Sulfonamide-resistant strains of Group A hemolytic streptococci appeared in the armed services of the United States during World War II.[23-28] Although it was recognized that the civilian population was exposed to these resistant strains (mainly Types 3, 17, and 19), no epidemics therefrom were reported until 1946, when an outbreak of sulfonamide-resistant Type 19 infections appeared in Cooperstown, N. Y.[29] A recent report on the incidence of sulfonamide-resistant strains of Group A hemolytic streptococci isolated from actively infected patients and carriers revealed only one strain, a Type 19, in 167 isolations.[30]

These reports indicate the infrequency of sulfonamide-resistant strains of Group A hemolytic streptococci in civilian populations. Yet a potential hazard from this source exists among individuals receiving small daily prophylactic doses of sulfonamide administered for the prevention of rheumatic fever recurrences.

From purely theoretical viewpoints, according to Hartman and Weinstein,[30] "these resistant bacteria could arise as naturally occurring variants; they could arise as variants of normally susceptible strains as a result of contact with and adaptation to the drug, or they could arise as spontaneous genetic mutants." Jennings and DeLamater[31] studied a scarlet fever epidemic of Group A, Type 17, sulfadiazine-resistant hemolytic streptococcus. They reported that they found evidence to suggest that the organism became resistant during the early phase of the epidemic in the face of sulfadiazine prophylaxis where small dosage produced ineffective drug levels and possibly promoted mutable organisms to develop drug resistance. In a discussion of epidemiologic problems as a result of human action Burnet[32] contends that there is no reasonable doubt that the appearance of these resistant strains of streptococci was directly due to the wide-scale use of sulfadiazine as a prophylactic drug.

Penicillin-resistant strains of Lancefield Group A hemolytic streptococci would be of considerable clinical significance, but reviews of the literature have not revealed a proved instance of increased resistance associated with a human infection.[33] Employing in vitro techniques Gezon reported increases in resistance varying from no increase to a seventeen-fold increase following sixty transfers onto media containing the highest concentration of penicillin permitting growth. In those instances where heightened resistance was observed, there was noted an associated marked loss of mouse virulence, loss of group-specific precipitinogen of Lancefield, and a reduction and variation of hemolytic capacity. Employing in vivo techniques[34] in embryonated eggs and in mice, no alteration in penicillin sensitivity was produced. There is considerable significance to be attached to the laboratory development of increased resistance of Group A hemolytic streptococci to penicillin if proved reduction of virulence results.[33, 35] These findings are at variance with the studies on sulfonamides where the virulence of the resistant strains remains unimpaired.[25-29, 31]

Milzer, Kohn, and MacLean[36] reported a high incidence of penicillin-resistant strains of hemolytic streptococci following the oral administration of 50,000 units of penicillin twice daily to inactive rheumatic children. Unfortunately, no attempt was made to group the isolated strains by the Lancefield precipitin technique. Based upon the reported frequency of the Group A hemolytic streptococci recovered by throat cultures, they assume that at least one-half of the resistant strains belong to Group A.

Studies of Markowitz and Kuttner[5] demonstrate that 50,000 units of penicillin administered orally to the fasting child produce serum levels varying from a maximum 0.25 unit per milliliter after one hour to 0.04 unit per milliliter after two hours. A definite bactericidal effect against standard C203 *Streptococcus pyogenes* was observed by Eagle[37] with a penicillin concentration of 0.006 unit per milliliter. The maximal rate of killing was obtained at a level of 0.064 unit per milliliter.

Studies[33] on 203 freshly isolated virulent strains of group A hemolytic streptococci from patients with acute upper respiratory disease, none of whom received penicillin, revealed a general lack of penicillin resistance (range from <0.01 to 0.02 unit per milliliter). Recent observations of Massell, Dow, and Jones[38] indicate that group A hemolytic streptococci isolated from the throats of carriers were sensitive to penicillin (range from 0.006 to 0.04 unit per milliliter). They were unable to explain why only 75 per cent of the carriers could be completely freed of the organisms when 300,000 to 1,000,000 units daily were administered for ten days. They consider the presence of tonsils to be a possible factor preventing such therapy from being 100 per cent efficient.

The present study was undertaken to evaluate the capabilities of oral penicillin in the prevention of Group A hemolytic streptococcal upper respiratory infections and the elimination of throat carriers in a children's hospital, the majority of the patients being chronically ill, rheumatic children. During the seven-month study, 8,500 doses of oral penicillin were administered. No untoward reactions of penicillin sensitivity[39, 40] such as skin manifestations (urticaria, angioneurotic edema, etc.), glossitis, diarrhea, arthralgia, or unexplained

febrile phenomena appearing on initiation of therapy or two weeks thereafter alleviated by drug discontinuance, etc., were observed. The ease of administration of penicillin and its general acceptance in candy form by the majority of the children compares favorably with any oral medication. Routine laboratory examinations of blood and urine to detect and correct any potential toxic manifestations arising from its use were unnecessary with oral penicillin as distinguished from the potential hazard associated with the sulfonamides, even though administered in minimal dosage.[41]

Except for its present high cost preventing its more general use, penicillin has many advantages over the sulfonamides in protecting against Group A hemolytic streptococcal infections. From the results of this study and the results presented in the discussion penicillin possesses greater antistreptococcic capacities than the sulfonamides. It has been employed with dramatic results in therapy for sulfonamide-resistant group A hemolytic streptococcal infections.[31] Recorded studies have not presented satisfactory evidence that penicillin-resistant group A organisms have appeared in human infections, nor has resistance been stimulated by laboratory efforts without loss of virulence.

An argument against the prophylactic use of oral penicillin may be advanced in the observation that the nonhemolytic, viridans streptococci and certain serologic groups of hemolytic streptococci other than Group A may become increasingly resistant to penicillin when such therapy is inadequate for their complete elimination. Such organisms are potentially capable, under certain circumstances, of causing bacterial endocarditis. Increasing amounts of administered penicillin would, therefore, be necessary to overcome infections resulting from bacteria possessing this induced resistance.

Oral penicillin offers considerable promise in the control of epidemics of upper respiratory infections among children in homes, schools, and other institutions.[42] The abundant evidence favoring its employment in Group A hemolytic streptococcal upper respiratory infections, however, offers great promise in protecting chronically ill rheumatic children from infections of this type. It appears that not all strains of these pathogens are capable of inciting rheumatic recurrences,[43] yet many are responsible for provoking reactivations or exacerbations of the chronic, active, rheumatic state.

It must be admitted that we do not possess conclusive evidence that deep-seated foci of hemolytic streptococci may not exist in inaccessible structures such as the tonsils, paranasal sinuses, and deep lymph nodes draining the upper respiratory passages. From the results of this report the dosage of oral penicillin employed was sufficient to eliminate group A hemolytic streptococci from the readily accessible mucous membranes of the mouth and throat.

This small study, while not conclusive, indicates that oral penicillin is a most satisfactory antibiotic in preventing group A hemolytic streptococcal upper respiratory infections. Additional planned and controlled studies directed toward protecting children with rheumatic fever are indicated.

CONCLUSIONS

Oral penicillin administered in the fasting state to chronically ill rheumatic children in equally divided doses (200,000 units per day) produces a satis-

factory therapeutic blood plasma level for approximately three hours following each administration.

Sixty-three children receiving oral penicillin over a seven-month period had no confirmed Group A hemolytic streptococcal upper respiratory disease, and one child was a confirmed carrier. Sixty-four children served as controls during this period; four had confirmed Group A hemolytic streptococcal upper respiratory infections and eleven were proved carriers.

Employing two techniques for the estimation of penicillin resistance in fifty-seven strains, there was no demonstrable increase in resistance among these strains during this brief study.

The employment of oral penicillin in prophylaxis against group A hemolytic streptococcal upper respiratory infections has been compared with the present status of the sulfonamides. Present knowledge regarding penicillin resistance is briefly reviewed.

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FURTHER STUDIES ON ORAL PENICILLIN IN THE PROPHYLAXIS OF RECURRENT RHEUMATIC FEVER

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IN AN earlier article[4] we discussed the theory behind the use of oral penicillin and the earlier studies using sulfonamides for the prevention of rheumatic fever. Most of these studies are predicated upon the idea that the rheumatic disease occurs shortly after an upper respiratory infection of one to three days' duration caused by particular strains of hemolytic streptococci, followed by a latent interval of one to three weeks during which some phenomenon, either allergic, immunologic, or otherwise takes place, subsequently followed by the clinical manifestations of the rheumatic infection in any of its protean forms (Hansen[5]). Holbrook[6] found as many as 50 per cent of certain susceptible persons had a recrudescence of rheumatic fever within two to three weeks following an upper respiratory infection. Hugh Morgan,[7] in 1943, reported that 90 per cent of youths in World War II who suffered attacks of rheumatic fever while stationed in army camps, had an immediate previous streptococcus infection with an average latent period of sixteen days before the symptoms of rheumatic fever developed. Massel, Dow, and Jones[8] found that at some army posts actual epidemics of rheumatic fever resulted when upper respiratory infections due to hemolytic streptococci were present.

From the above reports it would seem logical to assume that any agent which would effectively eliminate streptococci from throat cultures would prevent the development of rheumatic fever.

Most of the accounts on the use of oral penicillin for the suppression of hemolytic streptococci in the throat and upper respiratory regions reported in the literature have been favorable. The majority used fairly large doses. Thus Massell, Dow, and Jones[8] used 300,000 to 1,000,000 units daily. Ross, Burke, and Olansky[9] used 50,000 units every three hours for six doses on adults and children were given a total of 200,000 to 500,000 units. One 11-year-old child with subacute bacterial endocarditis was given 100,000 units every three hours for fourteen days. The authors claimed that the results do not differ materially from those with parenteral administration except for the larger dose required.

In contrast to these studies, the authors published the results of a series of forty-four cases in which one-half of the patients received penicillin troches* and one-half were used as controls.[4] All gave a history of rheumatic fever and some evidence of heart disease. The dosage was at first 1,000 units three times a day (1945 to 1946) and later increased to 5,000 units three times a day in 1946 and 1947. In this series we gave the penicillin troches in order to attack

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*The troches used in the previous series as well as in this present series are marketed under the name of Ledercillin Crystalline Penicillin G Troches, 5,000 units each. They were supplied by the Lederle Laboratories Division of the American Cyanamide Company, 30 Rockefeller Plaza, New York, N. Y., who also aided by a grant.

the streptococcus at the apparent source of the trouble and we found the dose sufficient to effect bacteriostasis but, nevertheless, weak enough not to produce a blood level sensitizing the patient to penicillin. No culture or penicillin determinations were taken in this series. Penicillin is preferable to sulfa drugs because the latter depend largely upon a blood level and require repeated leucocyte, hemoglobin, and differential blood counts plus urinalysis. Baldwin[10] states: "Despite our good fortune in not encountering serious toxic manifestations, it is to be emphasized that such should be watched for and that a total white and polymorphonuclear count should be followed for at least the first two months of the prophylactic therapy with sulfa drugs. The urine should be followed for albumin and red cells at regular intervals throughout the treatment."

Having seen the apparent prophylactic efficacy in the preceding series, inasmuch as none of the twenty-two children receiving penicillin troches developed rheumatic fever while four of the controls receiving placebos did so, we determined to run another series with observation of throat cultures and determination of penicillin concentration in the throat and blood.

In our new series, forty-four children were selected (similar to the group in the previous study. Twenty-two received the troches and the remaining twenty-two served as controls.

TABLE I. SUMMARY OF CASES STUDIED

	AGE IN YEARS		
	4-8	8-12	12-15
Penicillin	5 cases	10 cases	7 cases
Controls	6 cases	12 cases	4 cases
	CARDIAC DIAGNOSIS		
	POTENTIAL RHEUMATIC HISTORY	RHEUMATIC MITRAL DISEASE	CONGENITAL
Penicillin	5 cases	14 cases	3 cases
Controls	7 cases	12 cases	3 cases

Method Used for the Study of the Penicillin Level in the Throat and Blood.—For the determination of the penicillin level in the throat and in the blood, the procedure used was that of Cooke's published in the third edition of Levinson and MacFate's textbook on clinical diagnosis.[11] This method consists in diluting the serum (blood) or fluids with sterile saline and testing the sensibility of a standard *Staphylococcus aureus* culture not older than twenty-four hours.

In the case of the determination of the oral penicillin level, the bacteriologist encountered several difficulties. The first one was in devising a method of obtaining the specimen from the throat. This was solved by making the person hawk up secretions from the throat and expectorate them into a sterile Petri dish, avoiding as much as possible the saliva that accumulates in the front of the mouth. The second and more important difficulty, as far as the bacteriology was concerned, was the contamination of these secretions with all sorts of organisms at the time of expectoration. To avoid this, we used the new B.D. Swinny filter for small amounts of fluid, thus obtaining a sterile fluid for examination.

Cases Studied.—Almost all of the cases that were studied were of patients at the Children's Cardiac Clinic at the New York Post-Graduate Medical School and Hospital. Most patients gave a history of rheumatic fever. A few were congenital heart cases. While the majority showed definite cardiac lesions, a few were classed as potential cardiacs on account of the rheumatic fever history with no definite cardiac lesions thus far.

Time of Penicillin Troches in the Mouth.—The penicillin lozenges were administered one hour after meals to avoid contamination from food particles.

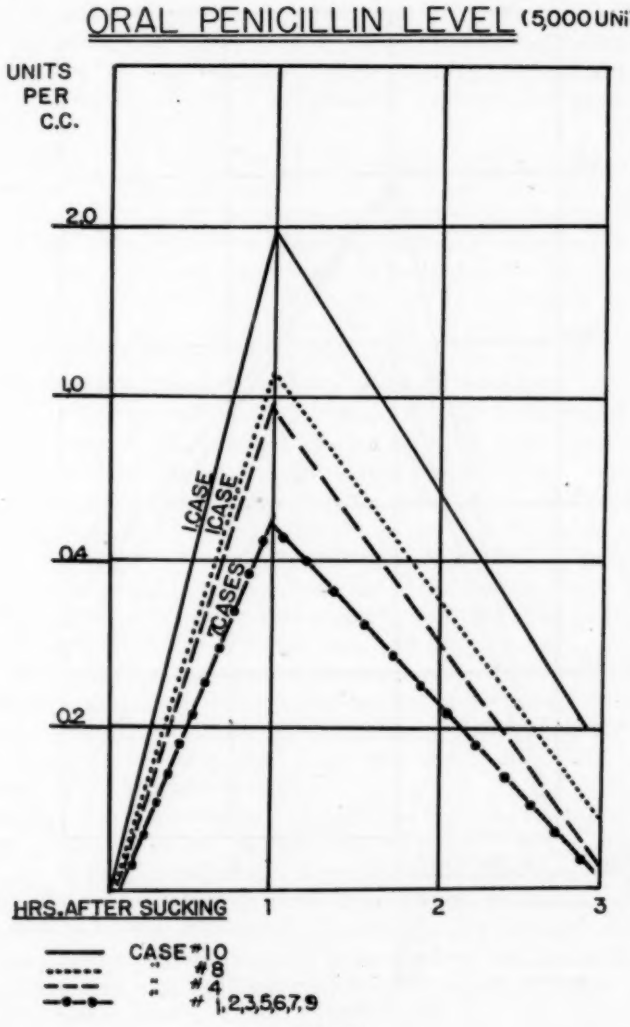

Fig. 1.

Each case was timed after the penicillin troches were administered to determine the minutes employed in sucking the troches. The longest took fourteen minutes and the shortest eight. The same time was consumed in the 5,000 units of penicillin as in the few cases receiving 10,000 units.

Penicillin Level in the Mouth.—Fig. 1 summarizes the saliva penicillin level in the cases receiving 5,000 units and Fig. 2, those upon whom 10,000

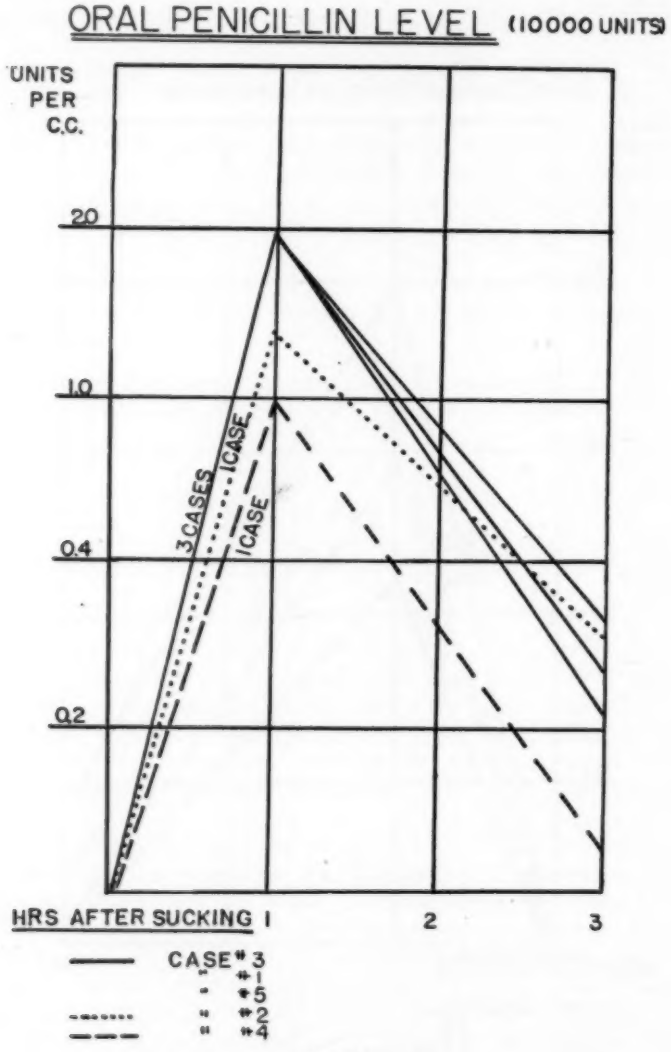

Fig. 2.

units were used. The results did not vary widely. While the 5,000 unit cases showed one who reached 2.0 units per cubic centimeter at the end of one hour, the 10,000 unit cases showed three who reached this level at the same interval. All the cases in both series exceeded 0.4 unit per cubic centimeter at the end of one hour. The level in all decreased substantially at the end of three hours. Some of the 5,000 unit cases neared zero and the one with the highest level dropped to 0.2 unit. The 10,000 unit cases showed an average level of 2.0 units per cubic centimeter at the end of one hour and at the end of the third hour an average of 0.2 to 0.3 unit of penicillin per cubic centimeter. As Rammelkamp and Keefer[12] have found that 0.3 unit of penicillin per cubic centimeter is the upper limit needed for bacteriostasis of susceptible bacteria, we found that there is a sufficient concentration of penicillin for oral bacteriostasis for almost three hours and that the 5,000 unit lozenge is adequate to maintain this.

Penicillin Level in the Blood.—Ten patients were studied to determine the penicillin level in the blood after the child had sucked penicillin lozenges. Five of these were given 5,000 units and five 10,000 units. In the 5,000 unit patients we found that in no case was there a sufficient concentration of penicillin in the blood to determine a level, even at the end of two hours. In the cases of those receiving 10,000 units, we found that two showed a blood penicillin level of 0.04 units per cubic centimeter at the end of the first hour. Two other cases showed the same level at the end of the second hour and one showed no penicillin level at the end of the first, second, or third hour.

We feel that 5,000 units is a sufficient dose, as it maintains an adequate throat level without establishing a blood level which might possibly desensitize the patient. Furthermore, the alternating high and low throat levels are desirable, as this results in preventing the growth of penicillin-fast organisms and also in allowing the growth of harmless saprophytes which might likewise have an inhibitory effect upon the growth of the harmful streptococci.

Nose and Throat Cultures.—Nose and throat cultures were taken during the eight months of study. At each monthly visit, the child received a general physical examination plus a routine nose and throat culture. If a growth of either *Streptococcus hemolyticus* or *Streptococcus viridans* appeared, the child was asked to appear for another culture within the week. If negative, the patient returned at the regular monthly visit. A sufficient supply of penicillin troches or placebo troches of similar size, taste, and shape to last one month was distributed to all the patients studied.

The results of this study showed four cases had a growth of *Str. hemolyticus,* thirty-four had one of *Str. viridans,* and four one of *Staph. aureus,* the rest showing nonpathogenic organisms. Three of the children receiving the penicillin troches had *Str. hemolyticus* in their throats at one visit only and only one of the controls had a like experience. Of those with *Str. viridans* culture, sixteen were receiving the penicillin and the other eighteen were controls. Of course, one must note that each child was instructed not to take a lozenge on the morning of the clinic session.

Two of the group harboring the *Str. hemolyticus* were Class III cardiacs who were bedridden most of the time and at the visit before beginning the penicillin lozenges throat cultures were taken and one hour later a penicillin lozenge was administered, to be followed at the end of a two-hour interval by throat cultures. Interestingly, the first cultures revealed a growth of *Str. hemolyticus* and the next two cultures were free from this organism, showing beyond doubt the efficacy of the troche. In the one case, a white girl of 12 years had had an attack of acute rheumatic fever and carditis each year for the past four years. This year, under the penicillin troche treatment, she went for the first time without developing any active signs of rheumatic fever. In our opinion the penicillin troche was undoubtedly an important factor in the prevention of rheumatic fever in this case.

In only one case was a positive *Str. viridans* culture found at a second visit.

All of our patients tolerated the penicillin lozenges very well. There was no mouth soreness nor discomfort at any time and there was no objection to taking the pleasant tasting troche.

CONCLUSIONS

Penicillin troches of 5,000 units each, when held in the mouth, are sufficient to produce a penicillin level of from 0.5 to 2.0 units per cubic centimeter of throat secretion at the end of one hour and retained a sufficient level to produce bacteriostasis of susceptible organisms for practically two hours.

The above process occurs without noticeably producing any penicillin level in the blood with the dosage described above.

By use of these penicillin troches the authors hope to prevent many of the *Str. hemolyticus* upper respiratory infections which are so frequently the precursors of recurrent attacks of rheumatic fever per se.

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PANCREATIC ACHYLIA AND GLYCOSURIA DUE TO CYSTIC DISEASE OF THE PANCREAS IN A 9-YEAR-OLD CHILD

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INTRODUCTION

CYSTIC disease of the pancreas at any age is an unusual finding. Except for cystic fibrosis of the pancreas in infants, there are not many cases reported. In a review of 6,708 autopsies at Guys Hospital in 1897, White[1] found only three cases of pancreatic cysts, and in 1921 Judd[2] reported forty-one cases of pancreatic cysts of all varieties from the records of the Mayo Clinic up to that date. The case to be presented and discussed is that of pancreatic achylia associated with glycosuria due to multiple cysts of the pancreas. We have been unable to find a description of a similar case in the medical literature.

CASE HISTORY

H. F. was a full-term, spontaneously delivered infant born June 13, 1938, weighing 5 pounds, 11 ounces. He was fed a formula of evaporated milk, Dextrimaltose, and water, and received supplementary vitamins from one week of age. There was no erythroblastosis or other apparent illness except hernias which were treated by truss. At 5 years he had measles and later the same year, mumps, without evidence of pancreatitis.

His father, aged 35 years, and brother, aged 5 years, are living and well. His mother, aged 35 years, has had five pregnancies. One newborn infant was an anencephalic monster, one was stillborn, and one died at 3 months of age of virus pneumonia. His mother has intermittently had glycosuria, and for three short periods had taken insulin. The first episode of glycosuria was twelve years ago; the second was after a miscarriage 11 months before the birth of our patient, and the third was during the second half of her pregnancy before the birth of the patient. She had no other illness during this pregnancy and the child showed no signs of hypoglycemia at birth. There is no history of other familial disease, including meconium ileus, cystic fibrosis of the pancreas, or polycystic kidneys.

The patient gained weight slowly and was always somewhat small in stature (Table I). Until his present illness, however, he was very sturdy and active. His appetite was always excellent. His caloric and vitamin intake was adequate. He had shown no intolerance to any foods. He had not had diarrhea, though his stools were frequently foul, nor had he been usually prone to respiratory disease.

In April, 1947, at the age of 9 years, the patient developed lower abdominal cramps and fever to 100.5° F. Six hours later he vomited. After being observed for twenty-four hours for possible appendicitis, he was admitted to a hospital with a diagnosis of intestinal obstruction. Laparotomy was performed. An irregular mass was found causing obstruction with impaction of feces from the splenic flexure to the duodenal-jejunal junction. Although this mass was thought by the surgeon to have no connection with the pancreas and to contain no large cysts, a biopsy was taken which was reported as "cystadenoma of the pancreas

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TABLE I

DATE	HEIGHT (INCHES)	WEIGHT (LB.)	AGE
June 13, 1938		5.7	Birth
Aug. 30, 1938	21½	8.0	7 weeks
Sept. 19, 1938	21½	8.6	10 weeks
Oct. 17, 1938	22⅝	10.2	14 weeks
Nov. 14, 1938	23⅝	10.9	18 weeks
Dec. 12, 1938	24⅜	11.7	22 weeks
Jan. 13, 1939	25½	12.6	26 weeks
Feb. 12, 1939	25⅞	13.3	30 weeks
Mar. 9, 1939	26⅜	13.4	34 weeks
June 3, 1945	43¾	35.5	7 yr.
July 9, 1945	44	38.7	7 yr. 1 mo.
Aug. 27, 1945	44⅛	38.7	7 yr. 2 mo.
Oct. 9, 1945	44½	41.2	7 yr. 8 mo.
Dec. 12, 1945	45	42.0	7 yr. 10 mo.
Aug. 20, 1946	47½	45.2	8 yr. 2 mo.
July 15, 1947		36.5	9 yr. 1 mo.
Aug. 15, 1947		36.7	9 yr. 2 mo.
Sept. 23, 1947		42.0	9 yr. 3 mo.
Oct. 15, 1947		42.2	9 yr. 4 mo.
Nov. 15, 1947		44.5	9 yr. 5 mo.
Dec. 15, 1947	47½	46.7	9 yr. 6 mo.
Jan. 15, 1948		52.5	9 yr. 7 mo.
Feb. 2, 1948		61	9 yr. 7½ mo.
Feb. 24, 1948		45	9 yr. 8 mo.
May 15, 1948	50	54	9 yr. 11 mo.
June 15, 1948		54	10 yr.
August 24, 1948		52	10 yr. 2 mo.

of unknown histologic nature and origin," without evidence of any inflammatory reaction. A normal appendix was removed and a cecostomy was also made at this operation.

The child made a good postoperative recovery and was discharged on the fifteenth postoperative day. The cecostomy was closing and the bowels were moving regularly, although no resection of the mass had been performed.

Ten days later the child again became acutely ill with nausea, vomiting, generalized abdominal cramps, and severe distention. He was afebrile. Diagnosis of intestinal obstruction was again made, and the cecostomy was reopened. Twelve hours later because of aggravation of abdominal pain and distention, he was reoperated upon. A volvulus with gangrene of 4 to 5 inches of ileum was found. The gangrenous segment was resected and the two ends of the gut were exteriorized. Further exploration was not done because of the patient's poor condition.

During his subsequent five weeks in the hospital, he lost 25 pounds despite "intensive treatment with whole blood, plasma, protein hydrolysates, and minerals."

Since a urinalysis had not been performed before the administration of intravenous glucose, it was not until all intravenous medication was stopped that it was discovered that his urine repeatedly contained sugar. In addition, it usually contained 1 to 2 plus albumin with few hyaline casts. The fasting blood sugar was 166 mg. per cent. Blood count, chest x-ray, and flat plate of the abdomen were normal. He received no insulin.

He returned home thirty-eight days after his operation and for the next three weeks ate very well but failed to improve. Although the cecostomy drained a small amount of watery fluid every few days, the ileostomy drained copious amounts of semifluid feces. The boy's psychologic adjustment to the ileostomy was good but he continued to be weak and severely emaciated and was, there-

fore, transferred to the Pediatric Service of The Mount Sinai Hospital, where he first came under our observation.

On admission on July 15, 1947, he was a pathetically emaciated, pale, chronically ill boy. There was marked wasting of subcutaneous tissue and musculature. He was too weak to sit up, yet he appeared unusually alert and intelligent. His axillary temperature was 99° F., and pulse 104, respiration 24, weight 36½ pounds (16.6 kilograms). There was generalized thinning of the hair, and the entire scalp, forehead, neck, and the eyelids were involved in a thick, dry, flaky, exfoliative dermatitis. Elsewhere the skin was similarly involved but to a lesser degree. The palpebral margins were thickened. His pupils reacted to light and accommodation. The fundi were normal. His lips were pale, but there was no cheilitis. His pharynx was bland and his tongue was not smooth. There was no general glandular enlargement. Examination of the chest revealed a few coarse râles over the left base posteriorly.

There was no impairment of resonance or fremitus, and no change in breath sounds. His brachial blood pressure was 90/60. The heart was not enlarged to percussion, the sounds were of good quality, and there were no murmurs. A sinus tachycardia was present. The abdomen was scaphoid and nontender. The liver, spleen, and kidneys could not be felt. There was a clean cecostomy in the right lower quadrant, draining a small amount of mucoid material. Just to the left and above the umbilicus there was a double-barreled ileostomy, from the proximal loops of which exuded semisolid feces. No abdominal mass could be felt. Rectal examination was negative. There was moderate clubbing of the fingers and toes. The deep tendon reflexes were hyperactive throughout, with unsustained ankle clonus. There was no disturbance of sensory perception.

Laboratory studies revealed: a white blood cell count of 15,400; segmented polymorphonuclears, 58 per cent, nonsegmented, 15 per cent; lymphocytes, 22 per cent; monocytes, 4 per cent; eosinophiles, 1 per cent.

The urine was yellow and acid, with a specific gravity of 1.024; it was albumin negative; there was one plus reducing substance identified as glucose; microscopically there were few uric acid crystals and no casts or cells; blood Wassermann was negative; Schick test was negative; Mantoux 1:10,000 was negative. X-rays of the chest, long bones and gall bladder showed no abnormalities.

Flat plate of the abdomen showed that: "Both kidneys are normal in size, shape and position. No urinary calculi noted or abdominal masses. No abnormality seen."

Intravenous pyelography showed no abnormalities.

Blood group was O, Rh positive.

Serum chloride was 91 meq. per liter; serum carbon-dioxide content, 27 meq. per liter; total serum protein, 6.3 Gm. per cent; hematocrit, 35 per cent; blood urea nitrogen, 10 mg. per cent; basal metabolic rate, plus 24 per cent Benedict-Roth (58 calories); culture of nasopharynx showed *Staphylococcus aureus* alpha and *Staphylococcus albus* beta; culture of ileostomy drainage showed *Bacillus coli*.

A barium enema revealed no obstruction of the colon up to the cecostomy. Examination of the lower bowel by passage of a Miller-Abbott tube inserted into the distal ileostomy demonstrated several loops of normal intestines. Thus patency of the lower bowel was proved and it was felt safe to let the colostomy close spontaneously.

A gastrointestinal series revealed a normal intestinal pattern down to the ileostomy, but when charcoal was given orally, it appeared in the ileostomy drainage in one and one-half hours. It was feared that this rapid transit time indicated a high ileostomy with a relatively small intestinal surface for absorption of food. Therefore a synthetic feeding was instilled into the distal ileostomy

segment by continuous drip. This consisted of a high vitamin, high caloric mixture of carbohydrates, fats, partially hydrolyzed proteins, and electrolytes, and provided one calory per cubic centimeter.

To demonstrate the absorption in the intestines proximal to the iliostomy, an oral glucose tolerance test was performed. The fasting blood sugar was 106 mg. per cent, with rise to 240 mg. per cent in one hour. Two subsequent glucose tolerance curves had fasting levels of 105 and 150 mg. per cent, respectively, increment rises of about 100 mg. per cent each after one hour, and gradual fall to fasting levels of the third hour (Table II). These studies demonstrated the child's mild glycosuria as well as his ability to absorb glucose.

TABLE II

DATE	DOSE GM. PER KG.	FASTING	½ HR.	1 HR.	2 HR.	3 HR.
7/18/47	1.75	160	200	240	145	100
10/29/47	2.5	105	185	200	125	100
11/11/47	2.5	150	---	260	250	50

To demonstrate the digestion and absorption of protein in the proximal segment of intestines, a gelatine tolerance test was performed, as described by West, Wilson, and Eyles.[3] There was practically no increase in the blood amino acids in five hours. This indicated either that there was no trypsin in the intestines to digest the proteins to absorbable amino acids, that there was insufficient area of intestines to absorb the amino acids, or, finally, that the transit time of the food from the mouth to ileostomy opening was too fast to allow digestion and absorption.

As closure of the ileostomy was imperative, the immediate problem was to build the child up for operation. It was, therefore, planned to feed him by mouth, by constant drip by tube into the distal ileostomy, and, in addition, by vein. He was given a high calory diet with supplementary water-soluble vitamins, and he received blood, plasma, protein hydrolysates, electrolytes, and vitamins. He also was given liver extract intramuscularly. He was given as much as 4,300 calories daily. Despite this tremendous intake for a 36-pound child lying in bed, he failed to gain.

The role his glycosuria played in his emaciation was raised. For one week he was given 5 units of protamine zinc insulin, then 5 units of regular insulin twice a day for ten days, after which the dose was increased to 10 units twice a day, but the glycosuria continued to fluctuate markedly and unpredictably. There was no acetonuria during this time. As there appeared to be no benefit from the insulin, it was discontinued.

The drainage from the ileostomy continued to be copious, and on one occasion, 800 c.c. of fluid were recovered in twenty-four hours by wringing out his ileostomy dressings. This must have represented a fraction of the total discharge, but represented 60 per cent of his oral intake, thus emphasizing the massive amount lost in this manner.

His stools were not weighed, but they too were large and contained an excess of starch and fat as shown microscopically. His failure to gain was, therefore, most likely due to impaired digestion aggravated by large ileostomy and cecostomy drainage.

Three weeks after admission, the boy developed an intercurrent pneumonia with temperature rise to 103° F. This was accompanied by a leucocytosis of 16,300. *Staphylococcus aureus* alpha and *Staphyloccus albus* beta were recovered from the nasopharynx. He was treated with aerosol and intramuscular penicillin. He improved but five days later developed jaundice. His urine showed bile and 1:40 urobilin. The icterus index was 16, blood bilirubin 1.0 mg. per

cent, Van den Bergh indirect positive, cephalin flocculation 3 plus, prothrombin index 48 per cent, cholesterol 130 mg. per cent, cholesterol esters 60 mg. per cent, and stool bile negative. No bile was demonstrated in the drainage from the ileostomy. It was thought this upset might have been due to an homologous serum hepatitis secondary to the blood and plasma he had received two and one-half to three months previously. He was placed on a low-fat diet and given 2.4 mg. vitamin K daily. Three weeks later after a mild course and loss of only 2 pounds, he recovered without clinical or laboratory evidence of liver disease.

During September, three months after admission and one month after hepatitis, the child's status remained unchanged. Because of his failure to improve, the child was operated on September 26 by Dr. John Garlock. At operation no mass could be felt. The pancreas appeared firmer than usual, normal in size, with tiny nodules throughout the whole organ. A biopsy was taken of the pancreas. The cecostomy was closed. The ileostomy was resected, an end-to-end anastomosis was accomplished, many bands and adhesions were lysed, and a Meckel's diverticulum was resected. All wounds were closed undrained.

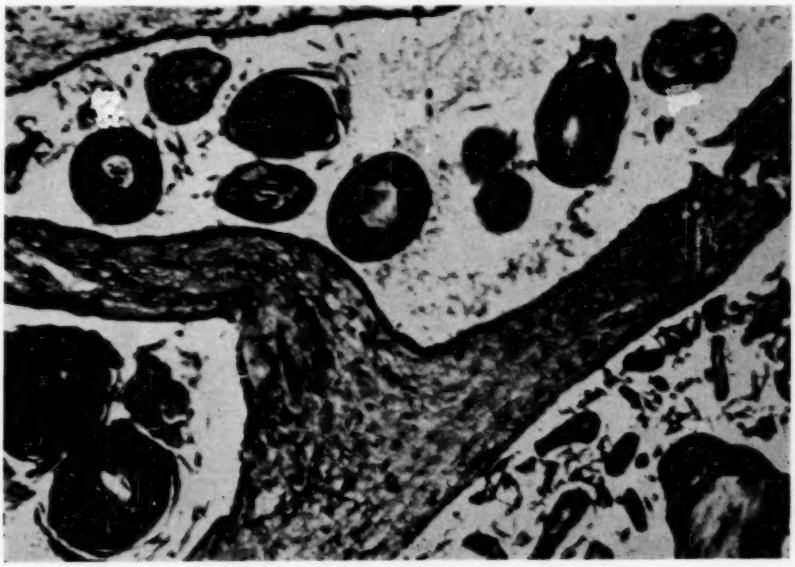

Fig. 1.—Microscopic section of pancreatic biopsy taken from patient revealing numerous cysts lined by low, cuboidal epithelium and containing pink-staining, laminated material.

Biopsy of the pancreas consisted of a 1.5 by 1.5 cm. mass of white, glistening, translucent tissue made up of closely packed, cystlike nodules measuring 1 to 3 mm. each. Microscopically these cysts were lined by low cuboidal and flattened epithelium and contained pink-staining, laminated material. (Fig. 1.) The cysts were separated by connective tissue septae, showing occasional structure suggestive of Islands of Langerhans. There was no inflammatory reaction, no extentensive pericystic fibrosis, no large cysts, and no calcium deposits. No typical acinar tissue was found in the biopsy specimen.

Postoperative recovery was complicated by severe right-sided pneumonia.

Despite the restitution of continuity of his intestinal tract, and even though he had a voracious appetite, the child failed to gain although his strength returned remarkably. A malfunctioning pancreas was thought a more likely cause for the failure to gain than was the small amount of intestines that had been removed, the low-grade chronic pulmonary infection, or the mild glycosuria. Studies of pancreatic function were, therefore, undertaken.

The blood amylase was normal, equivalent to 110 mg. of sugar. The stools microscopically showed fat and starch as well as undigested meat fibers. The dried stool fat was 48 per cent. The gelatin tolerance test was repeated. After the ingestion of gelatin there again was no rise in blood amino nitrogen. After the administration of glycine[4] a single amino acid not requiring further tryptic digestion, there was a prompt rise in blood amino acid nitrogen. This demonstrated a defect in protein digestion rather than impairment in absorption.

To demonstrate absorption of fat, a Vitamin A tolerance test was performed. After ingestion of 1 c.c. of oleum percomorphum there was a low fasting level of 31 gamma per 100 ml. and no apparent absorption of the fat-soluble vitamin. The fasting blood carotene was also very low, 15 gamma per 100 ml. It is also of interest that when the child was given an equivalent amount of Vitamin A in a water-soluble form (Mead's Polyvitamin Dispersion), he still showed essentially no absorption.

Dr. David Dreiling assisted us in doing further pancreatic enzyme studies. Under fluoroscopic control, a double rubber tube was passed into the intestines so that aspiration could be made simultaneously from the stomach and duodenum. He found that even after the injection of secretin, the patient had no increased pancreatic secretion. Only traces of lipase and amylase were found, and there was no trypsin present.

TABLE III. BLOOD

DATE	VITAMIN A	CAROTENE	VITAMIN C	TOTAL PROTEIN	A/G
7/14/47	37	11	1.28	6.86	3.33/3.53
10/21/47	Hrs. 31	15			
	4 35	15			
	6 33	14			
	8 20	14			
10/31/47	16	18			
	25	16			
	17	12			
	12	10			
12/19/47			1.21		
1/15/48				7.39	4.26/3.13
1/28/48	12	17			
4/13/48	34	17	1.21		

METABOLISM STUDIES

The patient was transferred to the metabolism ward* and there given a calculated high caloric, high protein diet without added vitamins. Urines and stools, the latter marked by charcoal, were collected daily and pooled for three-day periods. Urinary and fecal nitrogen were determined by the microkjeldahl method. Chemical analyses for urinary creatinine, amino acid nitrogen, thiamin, riboflavin and N'methylinicotinamide were done on the three-day pooled specimens. Urinary glucose determinations were made daily. Blood determinations for vitamin A, carotene, vitamin C, total protein, albumin and globulin fractions, glucose, and amino acid nitrogen were made as indicated.

Fig. 2 charts the results of the patient's weight, nitrogen and caloric intake, fecal and urinary nitrogen excretion, and nitrogen balance.

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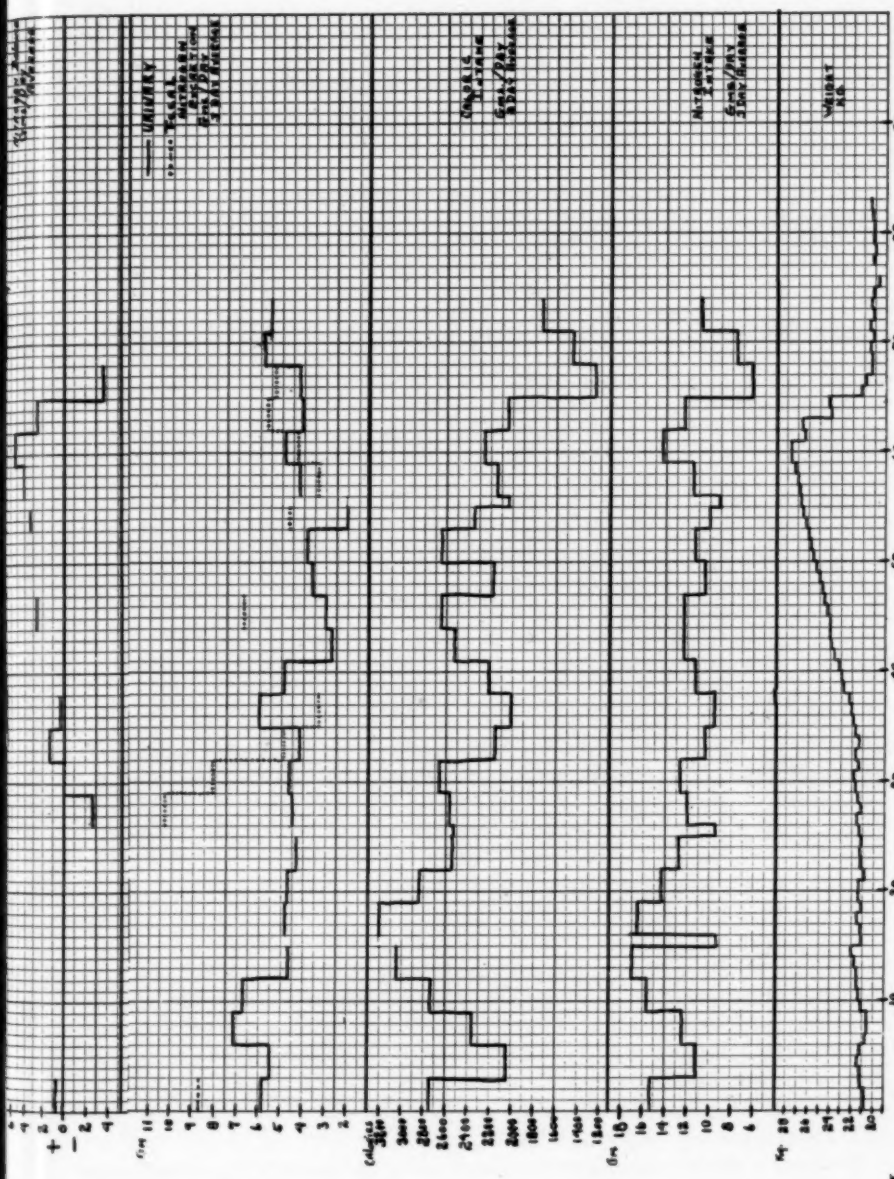

Fig. 2.—Nitrogen balance, urinary and fecal nitrogen excretion, caloric intake, nitrogen intake, and body weight. On the thirty-sixth day of the study, while the patient was taking 2.8 Gm. protein per kilogram body weight, he began to gain weight. This continued until he contracted an upper respiratory infection on the sixty-first day, when precipitous drop in body weight occurred.

During the first five weeks of study, the child failed to gain weight. During this period he was receiving an average protein intake of 82.5 Gm. per day or 3.9 Gm. of protein per kilogram of body weight per day. Both the fecal bulk and fecal nitrogen decreased during this weight-gain period, but never to normal levels.

From the thirtieth day to the thirty-sixth day of observation, the patient received daily doses of 3 Gm. of enteric coated pancreatin. Within one day it was noted that whole or partly broken tablets were appearing in the stools. It had been noted that when charcoal was given by mouth it usually appeared in the stools in four to six hours and therefore it was felt that the rapid transit did not allow the alkaline intestinal secretions sufficient time to dissolve the enteric coating. Plain pancreatin powder in various mixtures was refused by the patient because of its unpalatability. Beginning on the fifty-seventh day, the patient received 3 Gm. of uncoated pancreatin tablets daily. During this period his weight continued to rise and his nitrogen balance was better than before. However, on the sixty-second day, he began to lose weight rapidly and two days later an evident upper respiratory infection with temperature rise to 101.8° F. appeared. Râles rapidly appeared in both lung fields and he was given intramuscular and aerosol penicillin. During this period of eight days he lost 7.3 kg.

While on the Metabolic Service he required no insulin. His glycosuria generally ranged from 0 to 5 Gm. per day with an occasional increase to 10 to 12 Gm. Acetonuria was never present.

Urinary vitamin excretion studies revealed that on the adequate intake of dietary nitrogen the patient excreted normal amounts of thiamin, riboflavin, and N'methylinicotinamide during his entire stay. The vitamin A and carotene levels remained essentially unchanged from those done while the patient was on the pediatric service where he was receiving supplementary vitamin A. His blood levels of vitamin C remained high throughout his hospitalization. It is apparent that the patient's ability to absorb the water-soluble vitamins was not impaired.

CLASSIFICATION OF PANCREATIC CYSTS

The classification of pancreatic cysts has been varied in the medical literature and it is beyond the scope of this paper to enter that phase of it completely. However, Walter and Clagett[5] have organized a classification on an etiologic basis which is rather inclusive.

1. Cysts resulting from defective development:
   (a) Cysts among infants
   (b) Cysts associated with polycystic disease of the kidney
   (c) Dermoid cysts
   (d) Inclusion cysts
2. Cysts resulting from trauma (Pseudocysts)
3. Retention cysts
4. Neoplastic cysts
   (a) Cystadenoma
   (b) Cystadenocarcinoma
   (c) Teratomatous cysts
5. Cysts resulting from parasites

A perusal of this classification placed our case possibly in one of three categories: (1) cysts among infants, (2) retention cysts, or (3) cysts associated with polycystic disease.

(1) CYSTS AMONG INFANTS

Under this category are included cases of congenital cystic fibrosis of the pancreas. Although this disease has many different clinical features, it is obvious that our case does not fit into this group. This boy had a normal infancy and childhood with fair weight gain and absence of fatty stools or pulmonary symptoms. Although there are several cases of cystic fibrosis of the pancreas described in older children, they practically all reveal nutritional or pulmonary difficulties in infancy and only rarely has there been described an associated glycosuria. Parmalee[6] described a case of cystic fibrosis of the pancreas proved by autopsy in a 14-year-old child. She had had difficulty in feeding and steatorrhea in infancy but did well after 1½ years. At 11 years, however, symptoms recurred but there never was any associated glycosuria.

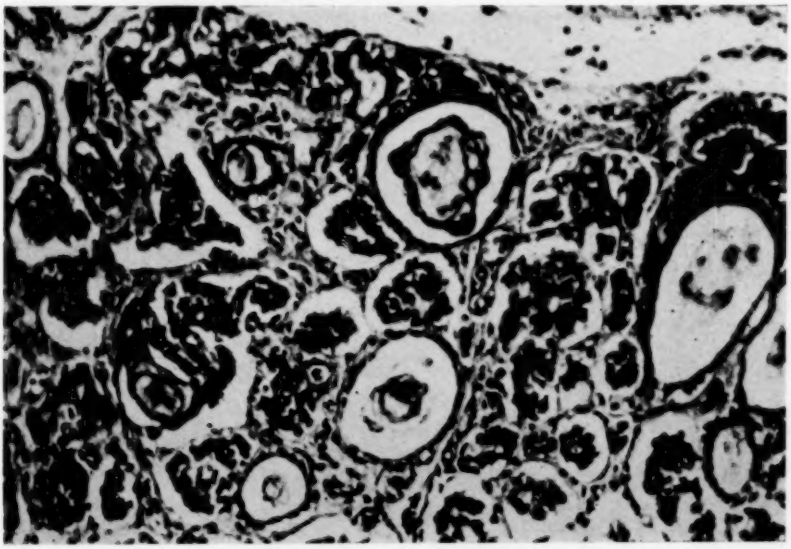

Fig. 3.—Microscopic section of cystic fibrosis of the pancreas revealing numerous small cysts with interspersed fibrotic changes. Islands of Langerhans are fairly numerous. This is to be compared with Fig. 1 for obvious dissimilarity.

Two biopsy specimens were taken from our patient at different times and neither one showed the characteristic changes seen in cystic fibrosis (Fig. 3). Microscopic examination of pancreatic tissue from cases of cystic fibrosis reveals much of the acinar tissue to be atrophic and replaced by proliferating fibrous and scar tissue, accompanied by varying amounts of acute and chronic inflammatory exudate. Islets of Langerhans are, as a rule, not significantly changed. In our patient (Fig. 1), there is no fibrous tissue interspersed between the numerous cysts. Although the two biopsies obtained account for only insignificant sections of the pancreas anatomically, still one can almost say with assurance that the rest of the pancreas must be similarly affected. Farber et al[7] reported two cases

of operative removal of approximately 70 to 80 per cent of the pancreas in children and in both these cases there was an adequate amount of pancreatic function present and diabetes did not occur. Lobbe, as quoted by Coope,[8] reported a similar case operated upon and later confirmed by autopsy. Of the whole pancreas in an adult only a stump 2 cm. long and adherent to the duodenum remained after an earlier necrosis. Even this shred of tissue was affected by inflammatory reaction, yet extensive metabolic studies were done and no real evidence of impaired digestion found. Thus one can safely say that when pancreatic achylia occurs, almost the entire pancreas must be severely involved.

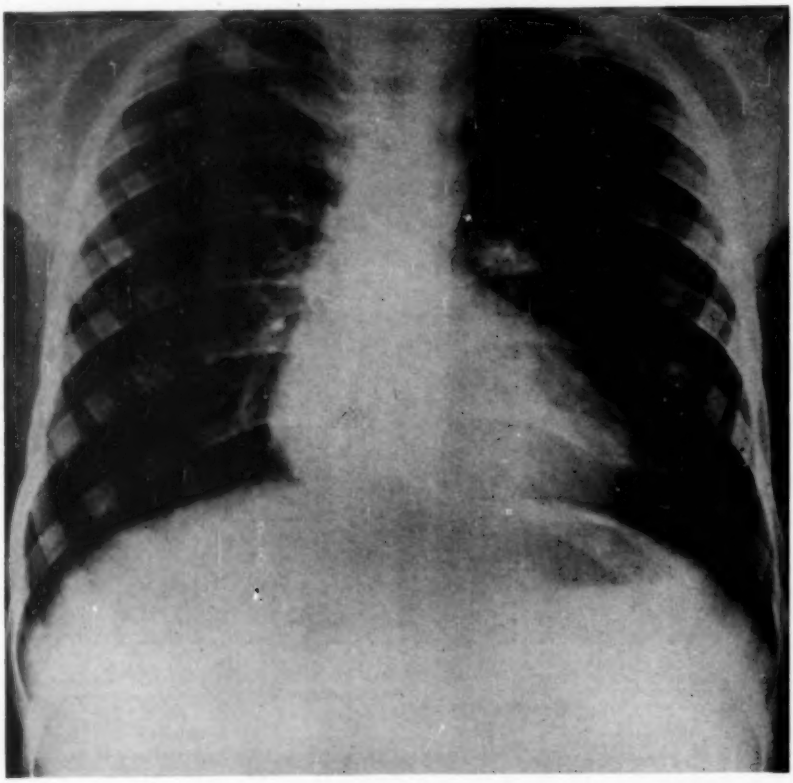

Fig. 4.—X-ray of chest revealing peripheral emphysema and hilar fibrosis.

(2) RETENTION CYSTS

Retention cysts have been described as resulting from an obstruction of larger or smaller ducts due to many causes. However, experimental evidence does not bear this out. Senn[9] considers, as a result of his experiments on animals, that the closure of the pancreatic duct is not the only nor the most important cause of the development of pancreatic cysts. Among all the cases of liga-

tion of the pancreatic duct which he performed on different animals, he never saw the development of a pancreatic cyst or any tendency to such formation, although without doubt the portion of the pancreas which was cut off continued to secrete, as was shown by experiments in which external pancreatic fistulae were established. The single visible result of the closure was always a moderate dilatation of duct beyond the ligature. The most important etiologic factor in development of pancreatic cysts, says Senn, must be sought in hindrance to absorption of pancreatic juice by the admixture of pathologic nonabsorbing substances or a lessened activity of the absorbing vessels. Farber[10] agrees with this view and feels it is the thick, gelatinous type of secretion seen in cystic fibrosis of the pancreas which primarily produces cystic changes. He proves this experimentally by repeated injections of pilocarpine in 6- to 8-week-old kittens, where pancreatic changes similar to those seen in cystic fibrosis of the pancreas were found to occur following these injections but not in control kittens.

(3) CYSTS ASSOCIATED WITH POLYCYSTIC DISEASE OF OTHER ORGANS

This is the rarest among cysts of the pancreas. Pathologists have used the term *dysontogenetic cysts* of the pancreas. This type of cyst occurs with other cysts of kidney, liver, and central nervous system. Lindau,[11] in his classic monograph, has described fifteen cases with polycystic disease of many organs. He found associated pancreatic cysts in eight of the fifteen cases and in two cases there was an associated glycosuria. In one microscopic section taken from a female adult the findings were similar to those in our case, but here there was no associated diabetes.

Although our patient reveals no clinical evidence of cerebral or renal cysts, yet the pathologic picture comes closest to that described by Lindau and probably falls in that group. There have never been any localizing cerebral symptoms in our patient and careful neurologic examination fails to reveal any evidence of cystic disease of the central nervous system. An intravenous pyelogram was also done and showed no abnormality of kidney or ureter.

The treatment of his glycosuria was never a complicated problem except for a short postoperative period when he developed acidosis which was easily treated with insulin and fluids intravenously. To date he is not taking insulin and intermittently spills 0 to 5 Gm. of sugar in his urine daily.

Whether this boy's glycosuria represented true diabetes is still open to question. It is true that he had three glucose tolerance tests which showed typically diabetic curves. However, his response to insulin was not typical. The other question that arises is whether he has had a subtotal destruction of his Islet cells due to pressure from cyst formation. This is only speculation and will not be gone into.

In cases of total excision of the pancreas[13] in adults there is usually a need of only 30 to 50 units of insulin daily. However, the amount of insulin necessary to control a child with complete excision of the pancreas has never been evaluated and conceivably is lower than this. It is also of interest that the patient's mother had mild diabetes while she was pregnant and this may have some bearing on the boy's pancreatic anomalies.

DIAGNOSIS OF PANCREATIC ACHYLIA

Pancreatic achylia gives rise to many specific findings and abnormal metabolic changes. However, many of these so-called "specific findings" have not been consistently diagnostic and it seems worth while to outline them with a brief discussion of their significance. The usually quoted findings in pancreatic achyliai are: (1) absence of pancreatic ferments; (2) steatorrhea and increased fat loss in the feces; (3) azotorrhea, increased nitrogen loss in the feces; (4) amylorrhea, increased carbohydrate loss in the feces; (5) flat gelatine tolerance test; (6) flat vitamin A tolerance test; (7) improvement of carbohydrate, fat, and protein metabolism with addition of oral pancreatic enzymes; (8) negative nitrogen balance.

1. *Pancreatic Ferments.*—The failure to demonstrate pancreatic enzymes upon duodenal aspiration does not of itself confirm the diagnosis of pancreatic achylia. This has been stressed by Bauman and Whipple,[14] who believe that only after the injection of secretin or mecholyl should one come to any definite conclusions. Secretin induces a copious flow of pancreatic juice which is rather poor in ferments, and mecholyl, which produces a neural stimulation of the pancreas through the vagus nerves, gives rise to a more concentrated and richer ferment mixture. Our patient upon direct aspiration of duodenal juice had only traces of pancreatic ferments which showed no rise following secretin injection.

2. *Steatorrhea.*—The presence of steatorrhea alone is not diagnostic of pancreatic achylia. Steatorrhea occurs in many conditions, among them being simple diarrhea, celiac syndrome, sprue, biliary obstruction, and prematurity. Our patient had steatorrhea with dried stool containing 48 per cent total lipids.

3. *Azatorrhea.*—Neither the increased percentage of nitrogen in the stools nor the presence of meat fibers is diagnostic of pancreatic achylia. As shown by Pratt,[15] the percentage of nitrogen in dried stools has proved to be of no definite value. There may be a relatively high content of nitrogen in the stool and yet the amount of dried stool may be so small that the absorption of nitrogen remains within normal limits. Beazell, Schmidt, and Ivy[16] have also found large quantities of meat fibers in stools of patients with simple diarrhea where the total fecal nitrogen excretion was only slightly greater than normal. With few exceptions, however, as shown by Beazell, et al,[16] pancreatic achylia is characterized by noticeable simultaneous failure in absorption of fat and nitrogen. Our patient had an increased stool excretion of both fats and nitrogen.

4. *Amylorrhea.*—The presence of starch granules in the stool is also not diagnostic of pancreatic achylia. The starch intolerance type of celiac syndrome as described by Herter,[17] Haas,[18] and Andersen,[19] frequently reveals the presence of starch granules. The failure of demonstration of starch granules should not make one hesitate to confirm the diagnosis of achylia pancreatica, since it is only infrequently found in these cases. Ptyalin, intestinal amylase, and colon bacteria are all instrumental in breaking down starch, and do it very well as a rule. In our patient fat droplets and meat fibers have been invariably found when he was on an unrestricted diet but starch granules on the contrary have only rarely been found in the stools during such periods.

5. *Gelatine Tolerance Test.*—This test, as has been shown by West, Wilson, and Eyles,[3] is specific of trypsin deficiency. It depends upon the ingestion of gelatin and the determination of blood amino nitrogen levels. In the presence of trypsin deficiency there is no rise of blood amino nitrogen. The question of impaired intestinal amino acid absorption should be ruled out by means of a glycine tolerance test[4] which uses glycine, a single amino acid, as the test substance, and then measures the rise in blood amino nitrogen. The absence of demonstrable tryptic activity by this test has only been found in cases of cystic fibrosis of the pancreas and pancreatic achylia. It was found in our patient.

6. *Vitamin A Tolerance Test.*—The finding of impaired vitamin A absorption can be used as a confirmatory test, but the poor assimilation of vitamin A is such a widespread finding as to make it nonspecific. There is a poor vitamin A absorption found in celiac syndrome, diarrhea, and even in certain allergic conditions. Two vitamin A tests using Oleum Percomorphum and Polyvitamin Dispersion showed impaired absorption in our patient.

7. *Addition of Pancreatic Enzymes.*—Although for the most part the addition of pancreatic enzymes orally has improved the digestion of protein, carbohydrates, and starches, and is considered by some authors as an essential feature, the literature is not entirely in agreement. Pratt, Lamson, and Marks,[20] Cruikshank,[21] Nasset et al,[22] Selle,[23] Schmidt et al[24] all observed a significant reduction in quality of nitrogen wasted in feces when adequate substitution therapy was tried. Coffey, Mann, and Bollman,[25] on the other hand, were unable to demonstrate any specific effect. In agreement with Seele,[23] the latter authors also found that enzyme therapy was without effect on the quantity of fat wasted in stool. Perhaps the reason for this disagreement may be the varying potencies of the specific enzymes in differently prepared preparations. Notorious is the low lipase content of most pancreatic preparations which accounts for the more frequent failure to improve the digestion of fat. Our patient did not show any striking improvement after the ingestion of pancreatic extract.

8. *Nitrogen Balance Studies.*—Studies of nitrogen balance are important in confirming the diagnosis of pancreatic achylia. Studies reported in the literature have been done on children with pancreatic achylia due to cystic fibrosis of the pancreas, and repeated observations have recorded the increased excretion of nitrogen in the stools of these patients.[12, 26] As a result of our metabolic studies, it was felt that our patient could be kept in good nitrogen balance and could gain weight if a liberal, high caloric, high protein diet was given. He consumed large amounts of food until he developed an intercurrent respiratory infection, at which point he rapidly went into a negative nitrogen balance and lost weight precipitously. While in "good health," he was in positive balance when taking only 2.9 Gm. of protein per kilogram body weight, and yet, at another time, while taking 3.4 Gm. of protein per kilogram body weight, he was in negative balance. This rapid weight loss and reversal of nitrogen balance associated with infection in these patients has been previously noted.[12]

SUMMARY

The case of a 9-year-old, previously healthy boy is described; he developed intestinal obstruction and at operation presented an abdominal mass, which on

two separate biopsies proved to be pancreas studded with multiple small cysts. Microscopic examination revealed a different lesion from that seen in congenital cystic fibrosis of the pancreas, but closely resembling that found in polycystic disease as described by Lindau. Extreme emaciation and evidence of vitamin A deficiency were present. These were accompanied by pancreatic achylia, failure to absorb vitamin A, flat gelatine tolerance test, and the presence of glycosuria. Clinical, chemical, and metabolic studies of the case are reported. In a follow-up after one year, the patient's general condition is good although his height and weight are retarded and he is prone to develop upper respiratory infections with rapid loss of weight. His mild glycosuria persists. Cystic disease of the pancreas and tests for pancreatic function are discussed.

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GRID PRODROME PHENOMENON IN CELIAC DISEASE

Report of Four Cases

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THE pediatrician in his modern role of practitioner of preventive medicine is becoming increasingly interested in eliciting the earliest possible signs of pathologic processes. The popularity of the Wetzel Grid method[1] for the study of the nutrition and development of individuals, gained in a relatively few years, attests to this concept of pediatrics.

Wetzel[1] early pointed out the beginning signs of simple nutritive failure, as mirrored on the grid by "cross channelling" and "low angle drift." We wish to present a preliminary report of similar changes in relation to the incipient stages of true celiac disease, clearly demonstrable on the Wetzel grid months before the onset of recognizable clinical evidences of this well-known disease entity.

We have termed this early phase of the disease the *grid prodrome*. Although seen in the form of cross channelling, it is best demonstrated in the auxodrome panel of the grid, usually manifest as a more or less sharp departure of the curve from the previously established auxodrome of preferential growth rate. In some cases another sharp dip occurs, denoting celiac crisis, soon after the onset of clinically recognizable signs.

The patients to be reported were studied in retrospect as part of a series to be reported in detail elsewhere.[2] No prediction can be made, therefore, as to whether or not the appropriate diagnosis could have been established during the prodromal period and the course of the disease thereby altered.

REPORT OF CASES

Case 1.—W. C., a white male infant, was delivered at term, weighing 6 pounds, 7 ounces. Weight loss and watery stools were first noted at the age of 6 months. He was admitted to Children's Hospital, aged 6¼ months, where the important findings included foul, foamy stools containing excessive amounts of fat and starch. A gastrointestinal x-ray study showed the moulage sign.[3] There was prompt clinical response to standard celiac dietary and vitamin therapy.

Fig. 1 illustrates this child's grid record. Here the grid onset antedated the clinical onset by two months, as indicated by the arrows.

Case 2.—C. R., a white female infant, the result of a normal pregnancy, was born at term weighing 6 pounds, 7 ounces. Intermittent diarrhea began at approximately 7½ months of age. At the time of admission to Children's Hospital, aged 9 months, she showed typical celiac stools and characteristic body conformation; the duodenal enzymes were normal in amount. She responded to routine therapy for a time but was readmitted at 11 months of age in severe celiac crisis associated with a respiratory infection. Thereafter, improvement was steady.

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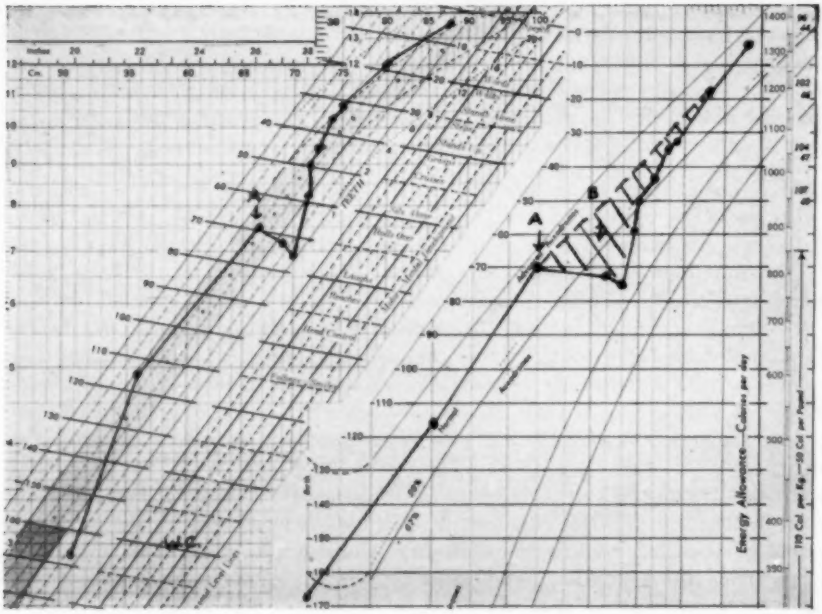

Fig. 1.—Wetzel grid record of W. C., showing grid onset (*A*) at age 4 months, as a sharp departure from physique channel and auxodrome. Clinical onset was at *B*, age 6¼ months. The interval *A*-*B* is the grid prodrome.

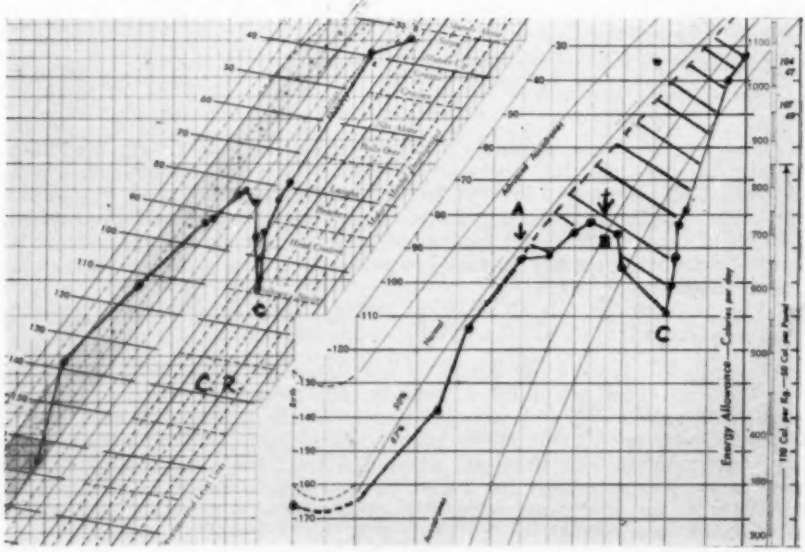

Fig. 2.—Record of C. R. on the Wetzel grid. The sharp departure from auxodrome at *A* is seen in the channel system only indistinctly. Clinical onset at *B*. Episode of celiac crisis at *C* is shown in the channel system as sudden weight loss. The interval *A*-*B* is the grid prodrome.

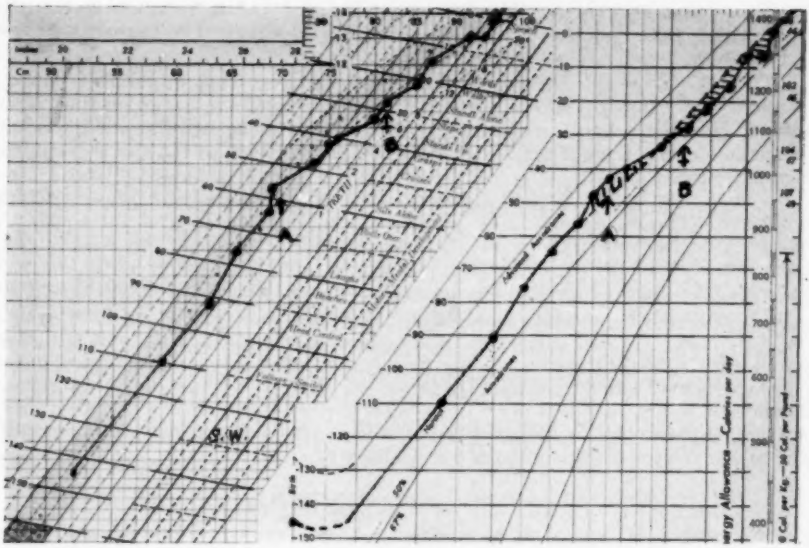

Fig. 3.—Record of S. W., a mild case of celiac disease. Grid onset at *A*, clinical onset at *B*; grid prodrome *A-B*. The brief episode of rapid weight gain preceding the grid onset has not been explained.

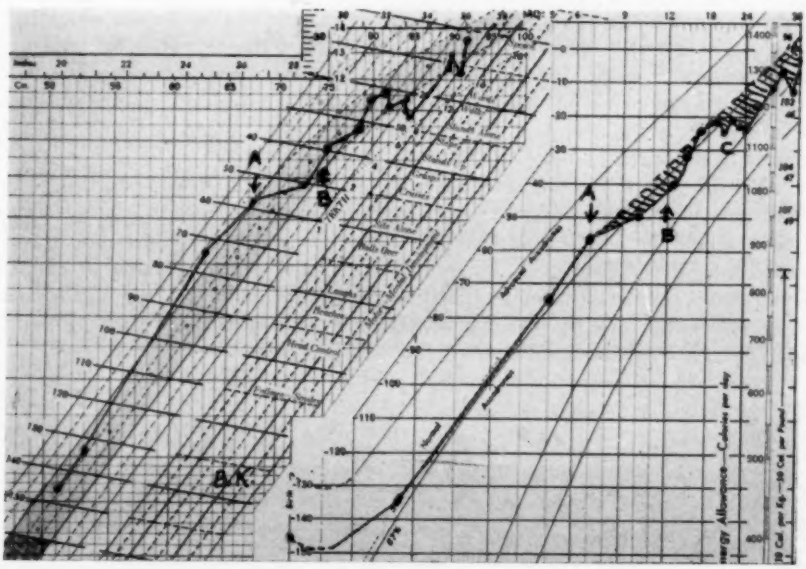

Fig. 4.—Grid record of B. K., showing grid onset at *A*, clinical onset at *B*, grid prodrome *A-B*, and first relapse *C*.

This patient's grid record is shown in Fig. 2. The arrows denote the grid onset which preceded the clinical onset by 3½ months. The episode of crisis at 11 months, associated with severe weight loss, is clearly seen.

CASE 3.—S. W., a white male infant, was born at term weighing 8 pounds, 1 ounce. He was believed to be well until 14 months of age, at which time intermittent diarrhea began. He quickly developed the potbellied habitus and characteristic stools. Except for minor setbacks, his response to routine therapy has been excellent.

Fig. 3 shows this patient's record, the arrows delineating the 5½-month prodrome. The initial period of weight gain, at the time of grid onset, and the relatively slight interference with linear growth as compared to weight gain, are unusual, and have not been explained on any basis other than the mild nature of the disease in this child, and probable imbalances in body fluid content.

CASE 4.—B. K., a white male infant, was born uneventfully at term, weighing 8 pounds. He had a brief episode of loose stools at 11 months of age, associated with a respiratory infection; by 14 months of age he had typical large, fatty stools and celiac habitus. He improved slowly on celiac diet, with several setbacks.

Fig. 4 shows this child's grid record, the prodrome lasting about 4½ months. The initial relapse at 19 months of age is also seen.

SUMMARY AND CONCLUSIONS

Four cases of typical celiac disease and their growth curves on the Wetzel grid have been presented. They illustrate the grid prodrome phenomenon, in that the onset of nutritive failure was demonstrable on the grid from 2 to 5½ months before the onset of recognizable clinical symptoms of the disease.

The mechanism of the prodromal phase is unknown. We might guess that it represents a stage of very subtle change in growth, ordinarily overlooked, and associated with the earliest workings of the defect in absorption of foodstuffs which occurs in celiac disease. We do not consider the grid prodrome specific for, or pathognomonic of, any one disease entity, but feel that it probably will be observed in the incipient and usually overlooked stages of other diseases, especially those of a metabolic nature.

The prodrome was not observed in all cases of celiac disease studied.[2] The exact incidence of this phase must be determined subsequently in a larger series.

It should be emphasized that the chief value to the pediatrician of such methods as the Wetzel grid lies in just such early warning signs as we have illustrated, in order to prompt him toward extra vigilance in his management of these patients, and by so doing to recognize the significance of the ordinarily ignored earliest clinical evidences of abnormal processes.

The assistance of Drs. Joseph S. Wall and William A. Howard in the preparation of this paper is gratefully acknowledged.

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STRICTURE OF THE URETHRA IN CHILDREN

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A URETHRAL stricture is a pathologic diminution of the lumen or of the distensibility of this canal. If we include the external urethral meatus (the pinhole meatus), congenital strictures are of extremely high incidence both in male and female children. One-fifth (over 1,000 cases) of the children I have seen because of urologic disturbances suffered congenital urethral stricture either as the fundamental lesion or as an important coexisting one.* Obviously the condition merits serious consideration among the more important lesions of childhood and especially since its neglect may entail grave renal damage. Acquired strictures are largely the result of gonorrheal infections and, though relatively rare, are of only slightly higher incidence than the traumatic variety.

CONGENITAL STRICTURE OF THE URETHRA

Pathology.—In the absence of infection, congenital urethral strictures are characterized simply by abnormal narrowing of the canal without localized periurethritis. These congenital narrowings are precisely similar to congenital strictures so often found in the ureters, biliary ducts, or gastrointestinal tract. Yet urinary infection commonly develops in these patients and with it periurethritis at the point of narrowing. This results in local leucocytic infiltration and ultimate laying down of a ring of scar.

The important as well as the vital pathologic consideration in urethral stricture is its effect upon the upper urinary tract and especially the kidneys, the ultimate destruction of which may be anticipated unless the obstruction is eradicated. Dilatation of the urethra proximal to the stricture ensues, and in some boys and girls with stricture of the meatus, we have found the entire urethra enormously dilated (Fig. 1). In some instances only the posterior urethra is greatly distended. In a 5-month-old boy, a large diverticulum of the anterior bulbous urethra nearly disappeared following wide meatotomy and dilation of the congenitally stenosed meatus. A diverticulum of the same cause was observed in a newborn male in the region of the frenum. As the obstruction persists and increases, the bladder becomes dilated and trabeculated (Figs. 2 and 4); increasing urinary back pressure causes the ureterovesical valve mechanism to give way. The ureters become progressively

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*A canvass of several urologists performing a large number of transurethral prostatic resections discloses that 8 to 10 per cent of these patients have a small meatus, presumably congenital and requiring meatotomy. In a smaller number there is urethral stricture in the absence of a history of urethritis or urethral trauma and, therefore, presumably congenital. In many other males a small meatus passes unrecognized until the acquisition of gonorrhea. Moreover, stricture of the urethra in adult females is an extremely common finding, the clinical manifestations of which usually cause the diagnosis of "cystitis" to be made, and often the history of the condition dates to childhood. In short, the fact that these congenital strictures cause no prominent symptoms in infancy or childhood may have been a detriment to the patient, permitting unrecognized, obstructive, uropathic changes to progress.

dilated laterally and, by longitudinal dilatation, elongated and secondarily kinked (Fig. 3). Hydronephrosis develops and, in advanced cases, the kidneys may be reduced to thin, scarred shells with little excretion. Unrelieved, the patient may be expected ultimately to die in uremia or urinary sepsis. In several cases of stricture of the external meatus, we have cystographically demonstrated wide dilation of the entire upper urinary tract

Fig. 1.—Cystogram in congenital stenosis of the external meatus in a 7-year-old boy. Bladder trabeculation is indicated by irregularity of contour; urethral dilation is extreme, especially in the posterior portion. Meatotomy cured.

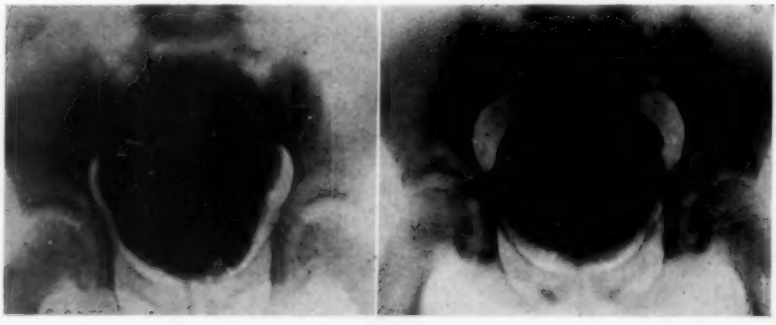

Fig. 2.—*A*, Marked sacculation of the bladder wall in a 3-year-old boy with congenital stenosis of external urethral meatus. Meatotomy. *B*, Cystogram two years after *A*. During this interval, the urethra of the stenosed meatus had been kept widely dilated. There is still cystographic evidence of the obstructive uropathy but the condition of the bladder wall shows marked improvement.

Fig. 3.—Congenital stenosis of external urethral meatus in an 18-month-old male infant with balanitic hypospadias. The bladder was chronically overdistended with 500 c.c. urine. Excretory urogram shows marked dilation of upper urinary tract, particularly left hydronephrosis and vesical overdistention. Meatotomy. Indwelling catheter was employed for two weeks.

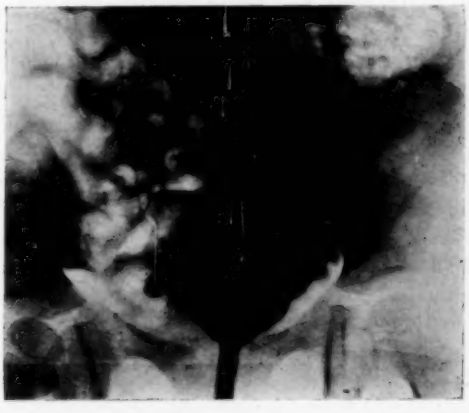

Fig. 4.—Vesical dilation, hypertrophy, trabeculation, and sacculation in a 13-month-old girl with congenital stricture of the anterior urethra.

(Fig. 3) which disappeared following simple meatotomy and the passage of sounds.

Symptoms.—The symptoms of congenital urethral stricture are predominantly those of obstruction with urinary difficulty, frequency, hesitancy, often terminal dribbling, and occasionally hematuria. The condition usually produces no symptoms until the second or third year of life, but may be manifest during early infancy. There is straining to void, the stream is extremely small, and with stenosis of the external meatus it may be threadlike and projected a great distance. Urination is sometimes intermittent and is generally painful. A recurrent, mucoid discharge may be noted. Hernia may result from excessive straining. A great many of the children the writer has seen with congenital urethral stricture were referred because of so-called enuresis, though with eradication of the stricture the dysfunction has usually disappeared.

With progressive renal injury by urinary backpressure with or without complicating infection, the systemic manifestations of urinary toxemia appear chiefly as gastrointestinal disturbances, anorexia, or failure to grow. Hyperirritability or sluggishness may result from toxic effects on the central nervous system. With the advent of infection there may be fever; the diagnosis "pyelitis" is usually then made.

Ulcerative meatitis is a frequent complication of congenital stricture of the urethral meatus in young boys.[1] There is superficial ulceration, a scab forms, this is wiped off by the clothing, and bleeding ensues. Parenthetically, it is this bleeding which, more than any other manifestation, is likely to direct attention to the condition. Healing occurs, the lumen is still further narrowed by the resulting scarring, and the cycle repeats itself. This condition has received considerable attention in pediatric literature, it having been believed by some that ulcerative meatitis results from dietary factors such as too much cream, while many have attributed it to the ammoniacal diaper with irritating urinary decomposition. Yet I have seen the condition in many boys long out of diapers and firmly believe congenital stenosis of the meatus is the basic lesion. The therapeutic test seems confirmatory for I have never seen a case of ulcerative meatitis which could not be cured promptly by wide meatotomy and maintenance of a wide open meatus. Although congenital stenosis of the external meatus is said to occur only in circumcised boys, I have seen it in the uncircumcised, but in the latter group there is no scab formation because the ulcer does not have the opportunity to dry. Most of the girls I have seen with congenital stricture of the urethra were referred for examination because of either persistent pyuria or so-called enuresis.

Diagnosis.—The diagnosis of stricture of the external urethral meatus in boys is readily made by observation of the pinhole-sized orifice. Yet in some of these cases the tightest portion of the meatal stricture is 2 or 3 mm. inside the orifice, and here the lesion is recognized at once by the passage of small sounds. Congenital strictures deeper in the urethra are diagnosed by difficulty of passage of small sounds, catheters, or bougies, and when the canal has been

adequately dilated to permit the introduction of a miniature urethroscope, the lesion may be visualized. In stricture, the instrument is grasped by the lesion. When the congenital stricture is located in the body of the urethral canal, it is often in the anterior bulbous urethra and may extend a centimeter or more. The bulbomembranous urethra is next in incidence as the site of congenital urethral stricture; congenital contracture of the bladder neck is fundamentally the same lesion—simply a congenital narrowing of the vesical orifice. In the extremely rare cases of congenital localized total occlusion of the urethra, there is an exaggeration of the same embryologic malformation in closure of the urethral gutter which produces congenital stricture.

The diagnosis of congenital urethral stricture in the female patient is suggested by difficulty of passage of small sounds which are grasped by the stricture. Yet the site and character of these strictures can readily be demonstrated by urethroscopy. If an irrigating type of urethroscope is used and this is recommended, there should be a small inflow of water at the time of the examination. Usually the strictured area will show rigid urethral walls and loss of striae and appear as a blanched, constricting ring, the surface of which may show congestion, desquamation, erosion, ulceration, or low superficial granulation. It may also show the trauma of preliminary instrumental dilation with bleeding. In the diagnosis of urethral stricture we prefer to employ small sounds rather than small bulbous urethral bougies, and try to confirm the diagnosis as often as possible by urethroscopy.

Treatment.—Congenital stenosis of the external meatus in boys is best treated by liberal meatotomy. This is readily performed in the office without anesthesia and if done quickly while the glans is firmly compressed between the thumb and first finger, is essentially painless (Fig. 5). Often the stenosed meatal opening is too small to permit the introduction of the tip of the knife blade, so that preliminary dilation with a probe or 4 F. or 5 F. sound is necessary. A No. 11 or No. 15 Bard-Parker knife blade serves admirably: the tip of the knife must be small enough to be introduced into the urethra at least 5 or 6 mm. Having widely incised the meatus downward, one can pass suitable-sized sounds to insure that the cut is adequate; the incised meatus of a 6-month-old boy should accommodate at least a 14 F. sound at the tip, and a 4-year-old boy should accommodate at least an 18 F. sound. Sounds of 10 F. and 14 F. should be passed to the bladder in these respective age groups to be certain there is no other congenital obstruction. Sharp-pointed scissors may be used for making the cut but the knife is my preference. Sutures are unnecessary. Brief, copious bleeding follows the incision but usually ceases shortly. Should it persist, this bleeding is readily controlled by compression of the glans for two or three minutes. No dressing is required following meatotomy although we customarily fasten a small piece of cotton over the end of the penis for thirty minutes until all bleeding has ceased. The object of this is to keep the child's clothing clean. The mother or nurse should be instructed to separate the incised surfaces of the meatus daily. After a week, the meatus should be widely dilated with sounds, and again in ten to

fourteen days, and at such times thereafter as may seem necessary to maintain a widely patent channel. The greatest difficulty encountered in the treatment of meatal stenosis is rapid healing together of the incised surfaces so that not infrequently a second meatotomy is necessary for a week or two. As in the treatment of all varieties of strictures, the condition is cured only when the strictured area remains widely and permanently dilated.

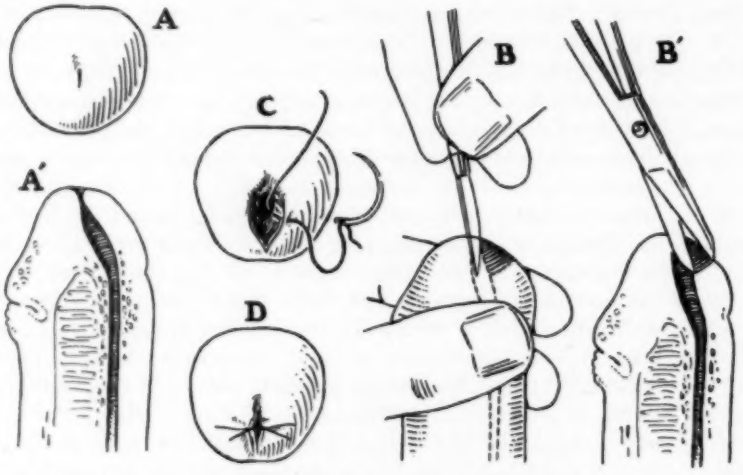

Fig. 5.—Meatotomy. *A*, *A'*, Minute meatus. *B*, Meatotomy with scalpel. If the glans is squeezed tightly simultaneous with the cut, the latter is almost always painless. *B'*, Meatotomy with scissors, but the knife is preferred. *C* and *D*, Suture of urethral mucosa to skin to prevent closure of the orifice healing, but this is unnecessary in children.

Congenital strictures located elsewhere in the urethra are best treated by dilation with sounds. Sometimes this means that the initial dilation must begin with an instrument as small as 4 or 5 F., gradually increasing the dilation as the caliber of the stricture permits, and without trauma. The urethra of the 6-month-old male infant should be dilatable at least to 10 F., and that of the 4-year-old male child at least to 14 F. The young female urethra will readily take sizes 2 F. to 3 F. larger. Stricture of the external meatus in the female practically never requires meatotomy and will almost always respond readily to periodic, progressive dilation with sounds.

Since the commonly employed curved or straight steel sounds regularly employed in adult patients are needlessly large and do not correspond in their curvature to the anatomic deep urethral curve of young male patients, the author devised a set of miniature sounds with short, sharply curved beak which represents a modification of the Van Buren sound adapted to the anatomic requisites of the young male urethra (Fig. 6*).[2] Because the urethra in the young girl is so short, I employ these miniature sounds in these patients as well.

*Manufactured by J. Sklar Manufacturing Company, Long Island City, N. Y.

Urethrotomy, either internal or external, should practically never be necessary for the treatment of congenital stricture in the young except in those rare instances of total or near-total occlusion of the urethra or, in short, when no instrument can be passed through the urethra to the bladder or dilation is unsuccessful. Yet occasionally the infant can be spared operation by gentle, forceful manipulation and good fortune on the part of the instrumenteur. In two newborn male infants aged 8 and 24 hours with complete occlusion of the deep bulbous urethra and distended bladder, a 6 F. sound was forced through the solid obstructing mucosal curtain, after which the urethra was further dilated to 8 F. and an indwelling catheter inserted for forty-eight hours. Subsequent periodic dilation was curative. If this maneuver is unsuccessful, urinary extravasation is almost certain to ensue and require prompt perineal urethrotomy, at which time the patency of the entire urethra can be established.

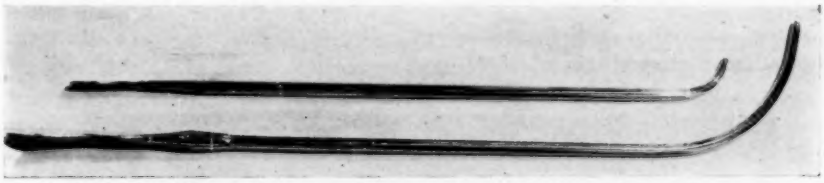

Fig. 6.—Campbell miniature sound compared with adult Van Buren instrument.

When the stricture cannot be penetrated, an exploratory sound is passed as far as possible into the urethra and the urethrotomy incision is made against the tip of the instrument, even though this may mean opening the pendulous portion. Following wide incision of the stricture, a catheter is left indwelling in the urethra for three days to keep the incised edges of the stricture ring separated. Beginning about the fifth or sixth day postoperatively, periodic, progressive dilation with sounds is employed to achieve and maintain adequate urethral caliber.

When the lumen of the congenitally occluded urethra cannot thus be established, prompt perineal urethrotomy or cystostomy should be performed at once to obtain free bladder drainage, and at a later date the urethroplasty necessary to construct a patent canal is carried out.

ACQUIRED URETHRAL STRICTURE

Gonorrheal urethritis accounts for most acquired strictures of the urethra in infants and children, but the nature of the lesion is often overlooked. A physician's 8-year-old boy was brought for examination because of enuresis. Despite his previous examination by several pediatricians and two urologists, a filiform caliber gonorrheal stricture of the anterior bulbous urethra had been overlooked (Fig. 7). With conservative, progressive dilation his symptoms promptly disappeared and ultimately the stricture was cured. The gonorrhea occurred at 2 years of age and presumably was a nurse-girl infection. The

pathogenesis of gonorrheal urethral stricture in the young is the same as in older patients. The columnar epithelium of the anterior urethra favors the growth and propagation of the gonococcus but stricture rarely occurs unless there is an intense, localized lesion with periurethritis, or treatment has been unduly traumatic. In the soft infiltration stage of periurethritis and stricture formation there is productive inflammatory reaction with subsequent organization of the exudate and the deposition of a variable amount of scar. There is slight sclerosis of the urethral walls as indicated by diminution of the normal folds and striae. This is the ideal time to achieve cure of the stricture by dilation with sounds. As the inflammatory process continues, there is further deposition of connective tissue so that the resulting scar must often be incised to achieve the desired urethral caliber. Urethral strictures, whether due to gonorrhea or nongonorrheal infections or associated with vaginitis, are often multiple and are almost always anterior to the membranous urethra. This scar manifests its inherent tendency to contract and insidiously causes grave urinary obstruction. Usually inflammatory stricture develops slowly, but in a boy with gonorrhea at 11 months of age a filiform caliber stricture at the penoscrotal junction was present at 22 months of age.

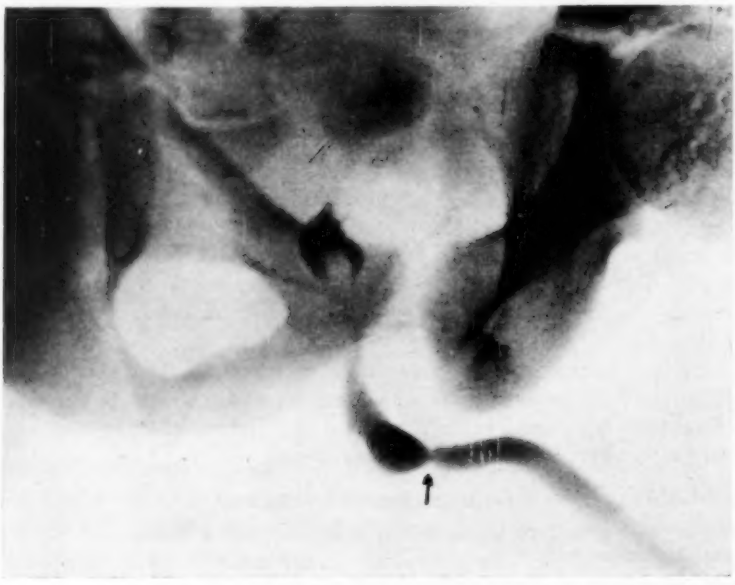

Fig. 7.—Postgonorrheal stricture in an 8-year-old boy examined because of enuresis; gonorrhea at 2 years.

The symptoms of acquired stricture appear insidiously with slightly increased frequency of urination later to be followed by urinary difficulty and terminal dribbling. The clinical manifestations and diagnosis are the same as described under congenital strictures. Treatment likewise is identical but gonor-

rheal stricture more often has to be cut, and if complicated by abscess, drainage is required. Stricture of the pendulous urethra not responding to dilation and not accompanied by periurethral abscess should be cut on the roof by internal urethrotomy. Deep bulbous or bulbomembranous strictures requiring urethrotomy are attacked by the perineal route. Yet even after surgical urethrotomy, the caliber of the urethra must be maintained by periodic progressive dilation until such time as the stricture remains fully dilated, for only then can it be considered cured.

TRAUMATIC STRICTURE

Most of these are the result of perineal straddle injuries or occur as complications of pelvic fracture. In children, the incidence usually follows the curve of traffic injuries. Straddle injuries most often involve the membranous urethra and there is frequently urinary extravasation immediately following the trauma. With healing of the traumatic lesion there is a residuum of dense periurethral infiltrate, and subsequent sclerosis forms the stricture. A young boy I saw had been hit in the penis with a basketball, causing rupture of the anterior bulbous segment with wide extravasation; stricture followed but was readily controlled by dilation. Since traumatic stricture always follows severe injury of the urethra, such injured patients should be observed and prophylactically dilated periodically for a number of years to be certain there is no interference with urethral drainage. Occasionally in localized traumatic stricture of the deep bulbous urethra excision of the scar-bearing area with end-to-end anastomosis of the urethra is successful.

Instrumental traumatic stricture of the urethra has been more commonly observed by me than any other form of trauma. This is due to failure of the instrumenteur to exhibit proper delicacy and gentleness in the passage of instruments as well as an absolute respect for the urethral caliber in selection of the size instrument he will employ. Several children have been seen with severe traumatic strictures of the bulbous urethra following cystoscopic instrumentation months or years before and, in at least two instances, I was responsible. Yet probably the greatest horror of this variety to come to my attention was a young boy whose urethra was densely strictured from end to end following cystoscopy months before in one of our leading medical institutions. Here a cystoscope entirely too large for this young boy's urethra had been employed, with a consequent ripping of the mucosa from meatus to bladder outlet. Parenthetically, trauma can be avoided in such a case by performing the cystoscopy through a perineal external urethrotomy opening. We have observed stricture to occur in some instances particularly at the meatus, following the protracted use of the indwelling urethral catheter.

Occasionally the urethra is injured by the self-introduction of traumatizing objects into the channel—pins, needles, sticks, glass rods, and so forth, in both sexes. In one instance, the mother tied a string about the base of the penis of a 5-year-old boy with acute gonorrhea, to stop the discharge. This resulted in penile thrombosis, periurethral abscess, urethral fistula, and filiform

stricture. The condition was corrected by removal of the constriction, wide incision of the thrombosed structures, and periodic, progressive dilation of the stricture with sounds.

Prognosis.—The prognosis of all types of stricture is dependent upon the pertinacity with which periodic dilation of the urethra is performed. With proper follow-through in these cases, cure of the stricture usually can be anticipated, but most patients with even moderately severe stricture should have the benefit of annual or even semiannual dilation for many years. Failing in this, operation, reoperation, extravasation, or fatal urinary sepsis may be expected.

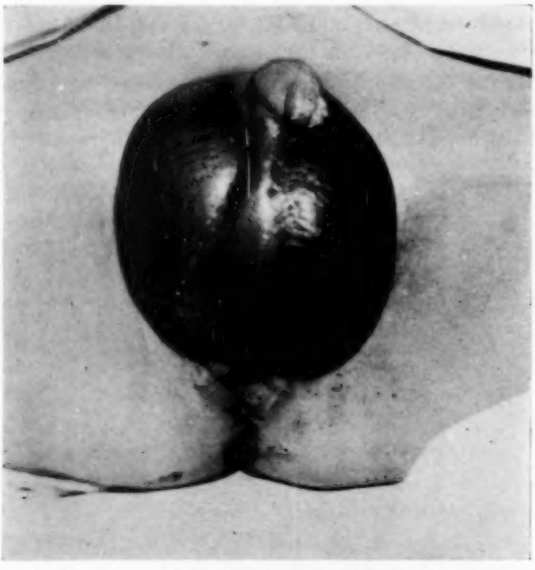

Fig. 8.—Extravasation occurring at site of surgical stricture following perineal closure of urethrorectal fistula in a boy of 7 years.

COMPLICATION OF STRICTURE

Ulcerative meatitis has been discussed. Acute periurethritis, even progressing to periurethral abscess, may occur at the site of stricture upon acquisition of fresh infection or exacerbation of a smoldering one, and particularly when there is increased urethral constriction or external trauma. Yet with the liberal employment of present-day chemotherapy and antibiotic therapy, such complications should occur rarely or not at all. If the condition remains a periurethritis, its resolution can be greatly accelerated by periodic urethral dilation. If the lesion progresses to abscess formation, external drainage and urethrotomy are necessary.

Fistula will rarely follow external urethrotomy if periodic dilation of the canal is maintained postoperatively. Even in the young, prostatitis regularly

accompanies urethral stricture, and epididymitis, acute prostatitis, or urinary extravasation occasionally occurs. Urinary extravasation is most likely to occur in the children with traumatic stricture (Fig. 8).

SUMMARY

If we include the congenital variety, notably of the external urethral meatus, urethral stricture is of high incidence in children of both sexes. Back-pressure damage of the kidneys, and particularly when there is complicating renal infection, is the vital clinical consideration in urethral stricture. As the narrowing and blockage increase the renal damage is accelerated. Symptoms of stricture are essentially the same in the congenital or acquired varieties and are fundamentally due to obstruction. Congenital stricture of the external meatus is readily recognized by inspection alone, and by gentle, intelligent instrumentation all varieties of stricture elsewhere in the urethra can be readily identified. The most satisfactory treatment is periodic, progressive dilation with steel sounds; urethrotomy seldom should be required in urethral stricture in children and almost exclusively for the treatment of the traumatic variety.

REFERENCES

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CONGENITAL ANAL STRICTURE

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CONTRARY to popular conception, congenital anal stricture or stenosis with its sequel of anal fissure or ulcer is comparatively common. Frequently missed for lack of systematic examination of the rectum in the newborn infant, these malformations may go unobserved. Daniels states that "unless they produce mechanical impediment to alimentation or become incompatible to life, they may not come to the attention of the attending physician; hence no accurate statistics are available."

In general, statistics on malformations of the anus and rectum point to an incidence of 1 in 10,000 births: but investigation will always show these figures refer to imperforate anus and rectum, or to congenital abnormalities existing between the anorectum and urogenital organs. As examples of statistical variations with reference to congenital anal stricture, Webb noted four cases in 150 consecutive deliveries, and Zahorsky found a palpable ring in fifteen out of sixty cases brought to his attention for anorectal complaints. Of sixty-one cases of anorectal conditions in infants and young children seen in my own practice during the past three years, the breakdown revealed:

Imperforate anus	1
Anal fissure	14
Anal ulcer	8
Anal cryptitis	12
Anorectal polyps	2
Prolapse of rectum	2
Congenital anal stricture	22

Accurate statistics on varying degrees of congenital anal stricture could be available only if a digital examination were performed on every newborn infant following delivery. The importance of such examinations cannot be overestimated; for it is only in the early stages that we may hope to remedy the cases of complete occlusion, and it is at this stage also that much can be done to prevent the minor malformations from proving serious in later life.

Tuttle states that the anus may appear perfectly normal on superficial observation, but examination will show it to be unusually narrow at some portion. This narrowing may take place at any point from the anal orifice to its junction with the rectum, or it may extend throughout the whole length of the anus. Since the length of the anal canal varies from 1 to 3.1 cm. with the lower limit prevailing in infants and young children, the impediment is found as soon as the finger is inserted into the canal. It may be at or just inside the aperture. In my own cases, the strictures were located anywhere from 1 to 3 cm. proximal

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to the anal orifice, with an average depth of 1.5 cm. The narrowing may be annular and very short, being formed by bands or membranes extending from one side of the anus to the other, or it may appear to have a sickle or diaphragmatic-like appearance. This condition differs from the narrowing of later life produced by pathologic causes in that there is no hypertrophy of connective tissue, no cicatricial tissue, and no hardening of the parts. The conditions attributable to inflammation develop after birth, owing to the passage of fecal matter through this abnormally narrow channel, with subsequent irritation therefrom.

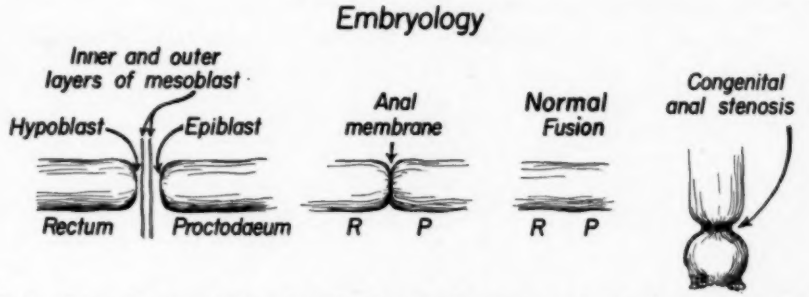

Fig. 1.—Schematic presentation of pertinent embryology in normal and abnormal fusion of rectum and proctodaeum.

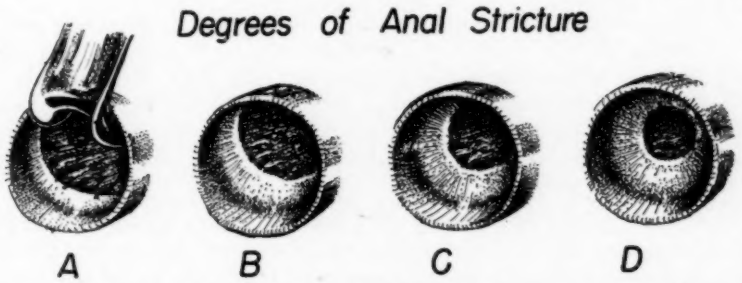

Fig. 2.—Schematic presentation of various degrees of congenital anal stricture.

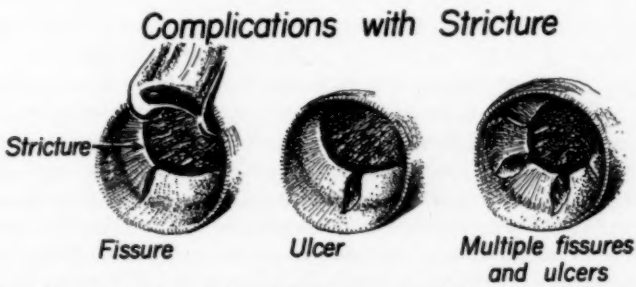

Fig. 3.—Schematic presentation of formation of fissures and ulcers secondary to congenital anal stricture.

The anal canal at birth ought to admit with comparative ease the little finger of a man's hand. When narrowing is pronounced one finds it difficult or impossible to introduce the finger through the contracted canal. These cases are the ones in which children are reported to have been constipated all their lives, and in which children frequently develop anal ulcers or fissures early in life due to tearing down of the stenosing tissue. Tuttle feels this condition should not be called stricture at the time of birth, because that term designates a pathologic narrowing of a canal which previously had been of normal proportions. It is true when these cases are treated later in life that the condition is one of stricture, referring, of course, to its origin and not to its pathology.

There can be no disagreement with Daniels' statement that "if one understands the fundamental steps in the evolution of the ano-rectum, one can almost visualize the various defects which might arise from arrested or faulty development as a result of imperfect obliteration of the proctodeal membrane." Crowell and Dulin state that "most anomalies are due to arrests or abnormalities of development arising in the 7th or 8th week of embryonic life. In the embryo of six weeks the cloaca is divided longitudinally by a down-growth of the uro-rectal septum. But for a time there is a small opening between the uro-genital tract and the hindgut, which is known as the cloacal duct. Failure of the cloacal duct to close accounts for the anomalous connections between the uro-genital tract and the rectum." Ladd and Gross state that "in the 22 mm. stage (late in the 7th week) a primary perineum is present. The perineum develops by the division of the cloacal membrane into the uro-genital membrane anteriorly and the anal membrane posteriorly, and by a down-growth and in-growth of the mesenchymal elements between these two membranes. Late in the 7th week, the uro-genital sinus has acquired an external opening, but the anal membrane does not rupture till later. A small dimpling of the anal pit forms the proctodeum, which inpocketing continues until the proctodeum and rectum join their lumina by rupture of the anal membrane."

This phase of the embryology may appear clearer to some readers by Tuttle's terse description: "the epiblast of the proctodeum (embryonic anus) and the hypoblast of the hindgut approach each other, and on conjunction form a double septum. The absorption of the septum renders the conjunction of the anus and rectum complete, and leaves a narrow zone that indicates the transition from mucous to muco-cutaneous tissue known as the pecten. This zone marks the lower limits of the rectum and the upper margin of the anus."

Congenital anal stenosis or stricture results from incomplete rupture of the membrane. Persistence of the membrane produces an imperforate anus.

Since most infants cry, have colic, and are more or less troubled with constipation or loose stools, these things are accepted for the most part as normal; and the parent, in consequence, does not go to the physician to have a rectal examination of the baby. Instead, nothing may be done, or else the formula may be changed, or suppositories, enemas, or cathartics given. And many times everything clears up quite well with such procedures. But when an infant at bowel movement continues to cry, draws up his legs, screams, and the stools

come out in a narrow, ribbonlike manner with evident signs of unusual straining or with a history of such constipation that might lead the physician to think he is dealing with a partial obstruction or Hirschsprung's disease, and when an older infant or young child similarly strains at bowel movements, cries, fears to go to the commode, has to be threatened or cajoled, or promised rewards, and may likewise have the type of constipation mentioned above, then certainly a rectal examination is in order. Often these little patients are dismissed by the general practitioner or pediatrician with a prescription for a suppository or change of diet; if this does not suffice, then in desperation laxatives or cathartics may be given. With negative results, the physician may discharge the patient as being pampered or of a neurotic type or he may vary the approach by saying the mother is overattentive and that either one or the other should see a psychiatrist. If the patient is not dismissed, the doctor will do a rectal examination and then find the anal canal narrowed: caused either by spasm due to an anal cryptitis, fissure, or ulcer, or else to a partially obstructing membrane of varying degree, the so-called congenital anal stricture or stenosis. The examination frequently reveals a fecal impaction above the narrowed zone. If a fissure or ulcer is found in conjunction with the stricture, the former is the result of a tearing down of the membrane secondary to pressure from straining during defecation, in an attempt to force the contents past the pathologically narrowed anorectum or anal canal. Most congenital strictures, unless found to be too thick, extensive, or unyielding, will clear up by means of dilatations. The stricture should be dilated daily with metal or gum elastic catheters, increasing the sizes to the point at which the little finger can be introduced. If, at the end of three to four weeks, considerable improvement is noted, then the parent is instructed to continue the procedure two to three times weekly up to six months. It is not always necessary to perform the dilatations daily, and many parents, after observing the procedure in the office a few times, are able to carry out the technique very well and capably at home, bringing the little patient to the doctor's office occasionally for check-ups in order to observe progress of the condition. If there is a concomitant superficial ulcer or fissure, it may be touched up with 10 per cent silver nitrate solution, which latter treatment is likewise sufficient for most superficial ulcers, fissures, or abrasions present in the absence of congenital anal stricture. If dilatations as outlined above afford little or no abatement of symptoms; or should the patient be in such a state that he cannot endure up to several months of dilatations, let alone the parents putting up with it, then it is advisable to resort to the following surgical procedure: effect multiple radial incisions of the stricture down to the external sphincter; free adhesions to the latter by running the points of a scissor between the sphincter and occluding membrane; and supplement postoperatively with dilatations twice weekly for two to three weeks. I would like to emphasize that in the technique I use no tissue is excised, and natural, painless movements occur in one or two days after the operation. Of the twenty-two cases of congenital anal stricture which I have seen in the past three years, eleven cleared up by dilatations, and the eleven which failed of such response were cured surgically by the method outlined. The patients referred who were subsequently operated upon had already

received the benefit of nonsurgical methods, with unsatisfactory results. Those sent for examination without prior treatment were always given a course of dilatations either by myself, the referring physician, or the parent, unless the extent of the condition did not warrant delay. Such cases as were improved by nonsurgical methods over a reasonable period of time never came to surgery. I would consider three to four weeks a reasonable length of time for nonsurgical treatment to indicate its worth. If little or no improvement is noted by the end of that period, continuing such methods for several months longer would hardly create any change for the better. The physician might be willing to continue further along this course, but not so the patient (who has very little to say in the matter), and surely not the parents, who have to put up with the infant or child at home.

CONCLUSION

Congenital anal stricture or stenosis is comparatively common, easy to recognize by digital examination of the anal canal, and just as easily missed because of failure to perform the examination. A rectal examination is always in order when the parent continues to tell the physician of the infant's or child's abnormal bowel habits. Owing to lack of reliable statistics inherent in the condition itself, one cannot state with any reasonable degree of accuracy the relative number of cases which clear up spontaneously, respond to nonsurgical methods, or are relieved only by surgery. Of twenty-two cases of congenital anal stricture seen by the author in the past three years, eleven, being resistant to nonsurgical treatment, were satisfactorily eliminated by a simple surgical procedure.

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TUBERCULIN PATCH TEST

Further Study of Modifications of the Normal Procedure

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IN A previous report,[1] it was shown that the efficiency of the tuberculin patch test was in direct proportion to the amount of autoclaving to which it was subjected, while all other variations attempted at that time had no deleterious effect.

In the present study, further attempts relative to variations in the method of applying the patch test were undertaken, among which were the following:

1. Keeping the patch for one and one-half years before testing.
2. Keeping the patch for four years before testing.
3. Keeping the patch for five years before testing.
4. Keeping the patch for five and one-half years before testing.
5. Keeping the patch for six years before testing.
6. Covering the patch with streptomycin solution (0.1 Gm. per cubic centimeter) and applying immediately.
7. Covering the patch with streptomycin solution (0.1 Gm. per cubic centimeter) for twenty-four hours and then applying.
8. Removing the patch after twenty-four hours.
9. Removing one patch after twenty-four hours and reapplying a second patch over the identical area.
10. Leaving the patch on for three days and then reading on the fourth day.
11. Leaving on the patch for four days and then reading on the fourth day.

As in the first report,[1] the patch sensitivity quotient (PSQ) was used to compare the sensitivity of each variation with the original patch test. In brief, this was arrived at by reading each test as varying from 1 to 4 plus; and then the sum of the regular patch readings was designated as the denominator and that of each variation as the numerator. A result of 1 or greater would indicate that there had been no deterrent effect, while any result less than 1 would indicate the degree of decreasing accuracy in doing the test under that given condition.

Listed in Table I is each of the eleven modifications, with each number corresponding to the variations as listed above.

From the Department of Pediatrics of the New York Medical College, Flower Fifth Avenue Hospital and Metropolitan Hospital.

TABLE I. EFFECT OF MODIFICATION ON PATCH SENSITIVITY

VARIATIONS	NO. OF TESTS DONE	PATCH SENSITIVITY QUOTIENT
1	7	.92
2	14	.75
3	4	.73
4	5	.80
5	7	.74
6	5	.95
7	5	.95
8	7	.94
9	7	1.50
10	6	1.00
11	6	1.12

In addition, it was decided to study the effect of elevated temperature of the patient on the patch test. Therefore, tests were done on the day of elevation of temperature and repeated when the temperature was normal for several days. Of twenty-three cases tested, twenty-one were negative and two were positive at the time of temperature and they remained so after the temperature was normal.

The effect of repeating patch tests on the same area in nontubercular infants was studied. As soon as one patch was removed, another was reapplied in the identical area. In eight cases, ten consecutive patch tests were performed in the above manner and all were negative. In two of the cases a dermatitis was noted in the region of the adhesive. In three of the cases patches were repeated in three and six months after the original testing and they persisted negative.

The effect of multiple or repeated patch tests on positive patch test cases was also reviewed. In this study, forty-three positive tuberculin cases were studied and the number of patch tests done varied from two to sixteen. In each case, at least two tests were done at one time and in twenty cases three were done simultaneously. In five others, four were done at one time and it was in one of the latter group that a reaction of temperature and generalized adenopathy was noted on the second day, and subsequently cleared up within one week. This gives a ratio of one reaction out of forty-three cases, or 2.3 per cent. These results are listed in Table II.

TABLE II. EFFECT OF REPEATED PATCH TESTS ON TUBERCULIN-POSITIVE CASES

NO. OF CASES	TOTAL NO. OF PATCHES PER CASE	NO. OF REACTIONS
18	2	0
15	3	0
3	4	0
2	6	1
2	7	0
1	10	0
1	11	0
1	16	0
Total 43		1 (2.3%)

DISCUSSION

Most of the modifications studied in this report were those that might be encountered in any hospital, clinic, or private physician's office.

It was noted that a great number of the patches that were one and one-half to six years old did not stick well and in those cases as well as any others demonstrating this defect, the patch was reinforced with new adhesive. Whenever there was a variation in the reaction of the two sides of the patch, the stronger reading was recorded. From the study it would seem that the age of the patch has some effect on the value of the test, since the PSQ dropped from 0.92 for those one and one-half years old to 0.75 for those four to six years old. Peculiarly enough, the results for the four- and six-year-old patches were almost identical.

Streptomycin in a dilution of 0.1 Gm. per cubic centimeter had practically no effect on the test, even when left in contact with the patch for twenty-four hours prior to its application.

Removal of the patch after twenty-four hours only affected the results very slightly, but reapplying another patch over the identical area accentuated the result. Removal of the patch later than the second day had no deleterious effect; if it was left on for four days and then read, the result was slightly accentuated. The presence of temperature did not appear to alter an individual's reaction to the patch.

Reapplying patch tests over the same area in nontubercular infants failed to produce any local sensitivity at the time, nor when repeated at three- and six-month intervals. This substantiates a previous study[2] in which patch tests were repeated every fourth day within a six-month period and no evidence of production of any sensitivity was detected.

Regarding reactions to the patch test, it was noted that out of forty-three tuberculin-positive children, only one developed a reaction; namely, temperature and adenopathy, after forty-eight hours. This cleared in one week. This reaction occurred in one of the cases that had had four patches applied at one time, which corresponded to our previous experience.[1] In the present study, the reaction was less than before, probably because fewer patch tests were done at one time. This would tend to caution one strongly against the use of multiple patch tests at any one time in a positive tuberculin case.

SUMMARY AND CONCLUSION

1. Fourteen modifications of the patch test were studied.

2. Patch test efficiency decreased with its age, being rapid at first and then more gradual.

3. Removal of a patch test after twenty-four hours lessened its accuracy slightly but reapplication of another patch in the same area or allowing the patch to remain on for four days resulted in an accentuation of the reaction.

4. Streptomycin applied locally over the patch had little to no effect.

5. Elevated temperature of the patient had no effect on the result of the test.

6. Repeated patch tests on nontubercular infants failed to stimulate any sensitivity.

7. Of forty-three tuberculin-positive children, a constitutional reaction occurred in one case (2.3 per cent) but cleared up quickly.

8. In conclusion, it can be stated that the patch test appears to be harmless to any nontubercular individual whereas in tuberculin-positive cases it should not be repeated unnecessarily, but more important yet is that multiple patch tests should be forbidden. Moreover, it would seem best to do the testing with patches that are not too old. If one were to be removed accidentally, reapplication of another for twenty-four hours would definitely confirm the results.

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LEPROSY, A DISEASE OF CHILDHOOD

With Special Reference to Early Findings in Eye, Ear, Nose, and Throat of Children Examined at the National Leprosarium at Carville, La.

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PEDIATRICIANS in the United States generally may be presumed to have had little opportunity to observe leprosy. Even in the endemic areas of this country they are likely to exclude it from their considerations, believing it to be a disease of adults. Physicians generally fail to realize that leprosy in all endemic areas of the world is continued principally through childhood infections. The histories of the majority of adult patients in this colony clearly indicate that their infections were well established before the age of 10 years, many having been admitted at the age of 5 years.

The eye, ear, nose, and throat manifestations of leprosy as seen in the children admitted to this hospital might be of value in distinguishing the protean rashes of leprosy from some of the childhood exanthemas and skin infections which leprosy often simulates. Before discussing these points of differential diagnosis it might be well to emphasize the importance of early diagnosis in all leprosy control programs. With the earlier recognition of leprosy children can benefit from treatment with the newer sulfone drugs and thus prevent the irreparable destructive complications of this insidious infection which might otherwise incapacitate them permanently.

SUSCEPTIBILITY OF CHILDREN

Muir[1] summarized the two generally accepted facts about leprosy in children when he stated that they are particularly susceptible to the disease and yet will not contract it if removed from the environment of the infectious parent at birth. Lara[2] believes that transmission by intrauterine means or breast feeding are doubtful questions but further observations are necessary before reaching conclusions. Both authors emphasize the danger in delaying the removal of the child from the infected home environment even for a few days. In a group of 260 leprous children of leprous parents, Lara found the first symptoms appearing in children under 5 years of age, manifest at approximately twenty months after exposure. Chiyuto,[3] reporting an extensive experience in the Philippines, concludes that most evidence indicates leprosy is continued through the particular susceptibility of children under 3 years of age, and believes the disease will continue indefinitely unless young children are protected. Manalang,[4] likewise experienced in the Philippines and Orient, emphasizes childhood as the period of infection and even goes so far as to deny vigorously the possibility of infection in adult life.

In this consensus on childhood infection we again refer to Chiyuto, who concludes that home isolation is inexpedient for many obvious reasons. He

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believes that no eradication or control effort will succeed unless the intimate and prolonged contact between the known adult cases and infants is eliminated. He emphasizes an important point, frequently overlooked, that the discharged negative patient is potentially just as dangerous to the susceptible child as the positive case because of a possible relapse.

EARLY DIFFERENTIATING SYMPTOMS

In children and adolescents leprosy often runs a course which may simulate rubella. (It may be of interest that Webster's Dictionary gives the etymology of "measles" as synonymous with Middle English leprosy, for in that period leprosy was prevalent in England.) The febrile episode of leprosy is known simply as a lepra reaction. The elevation of temperature to 104° F. or higher, together with general malaise and a rash of small macules over the face and extremities, may closely approximate the course and appearance of measles. One confusing example is that of a Negro boy 12 years of age who was excluded from school with "measles." After this early rash and the febrile reaction continued for several weeks the patient developed nodules as seen in Fig. 1. These alone were present on admission to this hospital.

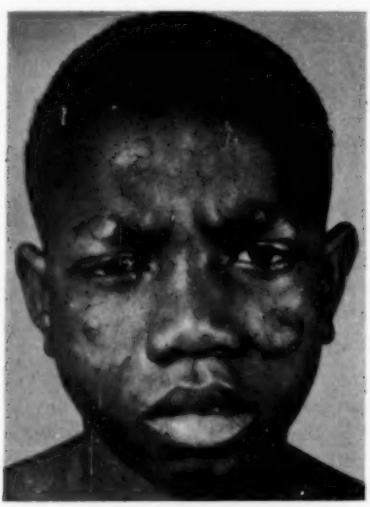

Fig. 1.—A Negro boy aged 12 years excluded from school with a diagnosis of "measles." Note the madarosis and edema of the nares. He lived in an endemic area (Texas).

There is no reference to leprosy in the family history. The mother died at the age of 30, and one brother and one sister died prior to the birth of this patient. All these deaths were from undetermined causes. In 1942 the boy was treated for "chicken pox." The distinguishing features of leprosy which might have been found on this boy even at that time are his ears, for the characteristic, full, pendulous lobes and the nodules on the auricle are indications that the disease has been long established. Likewise the swelling and tenderness about the tip of the nose and particularly the edema and infiltration about the alar

cartilages is almost pathognomonic. These indicators of nasal pathology together with a long-standing history of epistaxis, a very common symptom, should have led to an early inspection of the nasal cavity where the granulomatous mucous membrane over the nasal septum would have been found to be grossly infected with the characteristic acid-fast bacilli of Hansen.

These nasal symptoms are again demonstrated in Fig. 2 of a Negro boy admitted at the age of 11 years. The claim was made that the nodules on the hands and legs were of but three weeks' duration although he had multiple macules and induration of the face and brow. The family history is significant for his father was a patient at Carville.

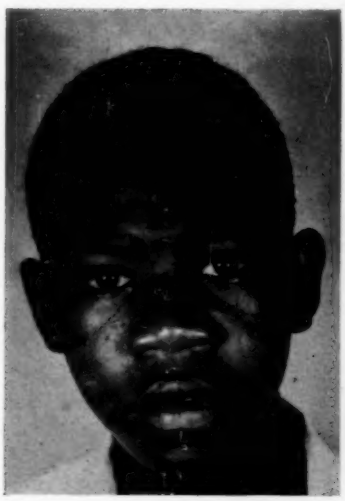

Fig. 2.

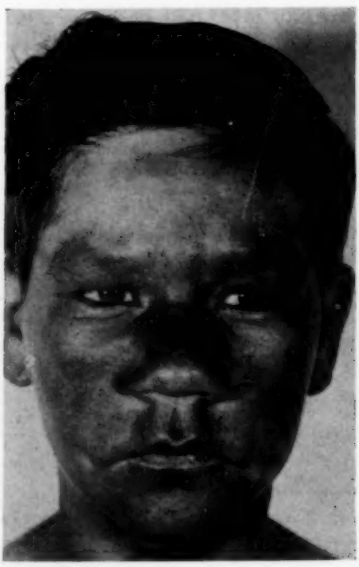

Fig. 3.

Fig. 2.—A Negro boy admitted aged 11 years, with a history of epistaxis, occlusion of nares, and edema of the tip, together with infiltration of the brow. His father has leprosy.

Fig. 3.—A white boy admitted aged 14 years, treated for "poison ivy" and "ringworm" for four years prior to the diagnosis of leprosy. Note the induration of face, edema of nose, and madarosis. He lived in an endemic area (Louisiana).

Madarosis is a finding which physicians can use in making a differential diagnosis. Our patient in Fig. 1 shows madarosis which was probably present even before the leprous lesions invaded the eyebrow. This loss of hair may include the lashes as well as the brow but is characteristically observed in the outer third or half of the eyebrow. It is generally bilateral. In the group of children in this study madarosis was seen in ten out of fourteen at the time of admission. It is our impression that when this condition exists leprosy has already been clinically active for as long as five years. Again in Fig. 3 madarosis is shown in a white boy admitted at the age of 14 years with

the advanced lepromatous form of the disease. The induration about the face, particularly about the eyes, nose, and ears, together with a lympho-edema of the extremities should have led earlier to a correct diagnosis. The eruption was first reported at the age of 10 years. The edema, together with the rash, misled the physicians, who treated the case at first as "poison ivy." As only a slight degree of success followed the local therapeutic measures and macules appeared, the diagnosis was changed to "ringworm." This boy had advanced nasal findings with a history of many attacks of epistaxis during the previous four-year period. A school physician commented upon his extremely enlarged tonsils, which probably showed a tenacious semiplastic material plugging the tonsillar crypts. This material was not caseous and was not expressed from the tonsils. A tonsillectomy was performed with a resulting exacerbation of all of the skin lesions. After a febrile period of a few weeks with no change in the macular eruption and general edema, a diagnosis of leprosy was made. This boy's family history, as reported, is negative to date, although he has resided in an endemic area since birth.

Fig. 4.—A Negro boy, admitted at the age of 11 years with a history of leprous lesions since the age of 3 years. Note the edema at the tip of the nose, induration of the brow, and nodules on the face. The mother and maternal grandmother have leprosy.

These characteristic changes of the loss of hair in the external margins of the brow and the induration in the face with the edema about the nose are again shown in Fig. 4. This Negro child admitted at the age of 5 years had a history of many episodes of rhinitis, epistaxis, and a macular eruption over the face and body since the age of 3 years. His mother is a patient in this hospital and his maternal grandmother died here. This family history, incidentally, shows the relentless continuance of leprosy through generation after generation when no control program exists to remove children from the infected environment immediately at birth.

There seems to be little pathology of the ear except for the characteristic skin lesions over the auricle and the large, pendulous lobes developing as the disease becomes established. We have not seen hyperaesthesia or anaesthesia of the external ear, nor have the children shown any thickening of the great postauricular nerve. There has been no nerve deafness in the group and only one child, a Mexican girl of 14 years, showed otitis media. This girl, though not admitted until recently, has had leprosy since the age of 5 years, her early lesions being of the lazarine, sharply circumscribed, hemorrhagic-necrotic type resulting in deep scarring. Oddly enough no loss of cilia or brow hair was observed. She showed advanced leprous changes in the auricle. Her ocular findings, however, were of special interest.

The conjunctiva were free of disease and there was no evidence laterally at the limbus of the episcleritis so often seen in patients who have had leprosy for more than ten years. On slit-lamp examination this girl showed the characteristic beading of the corneal nerves. Twelve of the fourteen children showed this phenomenon in each eye and a thirteenth showed it in the right eye only. These points of brilliance stand out on the shaft of the corneal nerves and seem to be an infiltration along the sheath representing in vivo and in miniature the infiltration of the peripheral nerves commonly seen in the more advanced stages of the disease. This beading is characteristically found in the corneal nerves of the superior and temporal quadrant, usually bilaterally. It is our belief that these findings indicate that the infection has been present for about ten years because the average age of this group is 11 years and the established diagnosis dates range from 3 months to 10 years prior to admission. This infiltration may be the only finding in an otherwise healthy cornea.

A punctate keratitis develops in these same areas of the cornea and is usually bilateral, following a symmetrical pattern in the superior temporal quadrants. It was found, however, in only six of the children in the group when studied with the slit-lamp. In young adults and more advanced cases the punctate keratitis together with an interstitial keratitis may be seen in these same areas but probably not before the disease has been established for fifteen or twenty years. The six children showing a nebulous microkeratitis in the substantia propria in the vicinity of the damaged corneal nerves had an average age of just over 13 years, the youngest being 11, the eldest 14 years old. All had the lepromatous form of the disease.

A vascular change at the limbus which is quite characteristic and which may be referred to as leprous neovascularization was found in eleven of the fourteen children. This is first recorded by Vale[7] in his work *Subsidiary Studies of Leprosy of the Eye.* Vale believes this vascularization may appear as a benign manifestation before any dermatologic symptom of leprosy exists. With the corneal microscope these capillaries can be seen to drain from deep within the cornea a rapid flow of blood and they unite over the limbus to form a large vessel concentric with and upon the corneal scleral junction. This again is laterally and along the superior temporal quadrant where this vessel

can often be seen with the naked eye. This leprous pattern is quite different from the normal radially disposed capillaries at the limbus.

An additional slit-lamp observation in this group of children is the frequent occurrence of filaments in the anterior chamber. These arise from the surface of the iris but should not be confounded with remnants of a persistent embryonic pupillary membrane. In eight of the fourteen children these filaments, generally incorporating particles of pigment, were found in the anterior chambers in many fantastic patterns. They were sometimes attached to the posterior surface of the cornea or might loop across the pupil to the opposite margin of the iris. Their attachments seem to be upturned sections of the mesodermic layer of the iris frequently rolled back for some distance along the margin of the pupil or punched out in moth-eaten patterns. Some eyes showed pedunculated free ends of this iris tissue waving like hydra in the aqueous. This finding occurred in about 60 per cent of the children studied, and is, we believe, a complication seen within the first few years of infection, for it was a prominent finding in a child 4 years old.

In none of the children have we observed the "pearl" formations of leprous iritis which are commonly seen in adults with a lepromatous form of the disease. The one possible exception to this was the 14-year-old girl who has had leprosy since the age of 5 years, but has had no sulfone treatment. In the extensive network of filaments in her right eye there are small semigelatinous masses on the iris at the point of attachment of the filaments. These are neither waxy nor white, yet in form are similar to the discrete "pearls" of leprous iritis seen in more advanced cases. This child likewise showed the only evidence in the group of serious involvement of the lens. On the posterior surface of the lens of the left eye there was seen with the spot beam of the slit-lamp a cluster of small, white nodules similar to those observed in leprous iritis. In three other children the only changes on the lens were particles and granules of pigment which were not remarkable. In none of the children was there any impairment of normal visual acuity.

Normal fundi were found on ophthalmoscopic examination in twelve of the fourteen. However, in a female white child 4 years of age a distinct patch of choroiditis approximately 3 mm. in diameter was noted nasally in the left eye. In a similar area and again in the left eye a patch of choroiditis was seen in a white boy of 13 years. This is considered by some writers as a sign of latent leprosy.[8] It is interesting that this 4-year-old child presenting the choroiditis had a most lavish display of wisps and filaments in her right eye only, but she showed beaded corneal nerves in each superior temporal quadrant and an extensive epicorneal vascular network in these areas. Dermatologically she had but one maculelike area which did not show bacilli in the biopsy, but which histologically was reported as leprous in character. This rather well illustrates Chiyuto's[5] contention that it is an error to depend exclusively upon the demonstration of acid-fast bacilli for the establishment of the diagnosis to the exclusion of clinical-pathological findings and a family

history that is positive. This child's mother has moderately advanced, lepromatous leprosy.

CONCLUSIONS

We wish to stress the importance of early diagnosis as an essential feature of any public health approach to the control of leprosy, and to emphasize the need for disseminating to all physicians in endemic areas medical information upon the earliest symptoms of leprosy, particularly in children. While the ultimate control of leprosy undoubtedly involves the removal of children at birth from the infectious environment, clinicians interested in the individual child must be more familiar with the disease in order to give their patients the benefits which may accrue from early treatment with the sulfone drugs.

Our findings and observations are limited to the small group of fourteen children admitted to the National Leprosarium in the last two years, and cannot, therefore, compare with the observations of other workers in those parts of the world where the truly early manifestations of leprosy in infants and children under 3 years of age can be studied. It might be misleading to assume from our limited illustrations that leprosy in the children of the United States is restricted to boys and is predominantly in the Negro. This is not the case, for in this group of fourteen children there were eleven boys, six being white, and all three of the girls were white. The fact that so few girls are admitted to this hospital rather indicates the widespread practice of retaining girls within the family until such time as the extensive complications of the disease compel the family to seek complete hospital care. Most writers report in the Philippines the infection rate in children under 5 years of age as being the same for both sexes.

In a differential diagnosis of leprosy from other chronic skin diseases or some of the common exanthemata of children an ophthalmological study is of considerable value. Even without access to such consultations the pediatrician and general practitioner in areas where leprosy is endemic should become more familiar with the common and characteristic external manifestations of this disease, particularly as seen in the eyebrows, ears, the eye, and the nose. In addition they should remember that in families where a case of leprosy is known to exist all younger members should be carefully scrutinized and observed for a period of years as the incubation period of leprosy is unknown, extending in some cases to a period of twenty years.

Although intensive therapy with the sulfone derivatives may be of great benefit to the individual child, it should be emphasized again that treatment alone will not by any means prevent the spread of this disease. As Muir[6] emphatically states, leprosy would die out of an endemic area within two generations if all children were kept free from contact with either known positive cases or so-called negative-discharged patients.

SUMMARY

1. An abstract of prevailing opinion concerning the special susceptibility of children to leprosy emphasizes the continuation of this disease primarily as a disease of childhood.

2. The diagnostic features and distinguishing characteristics of leprous lesions about the eyes, ears, nose, and throat with which the physician should become familiar are cited with illustrations and case reports.

3. In endemic areas in the United States leprosy appears to be a disease of childhood generally acquired before the age of 5 years.

4. If erroneously diagnosed or if recognized but hidden in the family, these cases may be foci for exposing other children in the community.

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POTASSIUM BROMATE POISONING

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THE effects of ingestion of bromates on man have received little attention in the medical literature. Two fatalities with severe kidney damage have been reported.[1, 2] It is the purpose of this paper to report three patients showing varying degrees of toxicity due to ingestion of potassium bromate. The first showed severe toxic nephrosis with anuria, the second mild renal irritation with oliguria, and the third gastrointestinal irritation with no evidence of kidney damage.

CASE REPORTS

CASE 1.—E. W., a 3-year-old white male child, was admitted to the pediatric service of Colorado General Hospital on June 11, 1947. Six days prior to admission he had ingested an undetermined quantity of permanent wave solution neutralizer, followed by vomiting, diarrhea, and virtually complete anuria. He had not been febrile. On the day of admission his parents noted that his face appeared puffy. His past history and family history were noncontributory.

The physical examination was normal except that the child appeared slightly ashen, hyperpneic, and his face was puffy. No pitting edema was present. Laboratory findings on the day of admission were as follows: blood sugar 205, nonprotein nitrogen 225, urea nitrogen 170, creatinine 25 (all figures represent milligrams per 100 c.c. of whole blood). Serum chlorides were 89 meq. per liter, and serum carbon dioxide was 6.7 meq. per liter. Hemoglobin was 10.2 Gm.; red blood cells, 3,780,000; white blood cells 7,200. Analysis of the initial urine obtained on June 13 showed 2 plus albumin, a trace of acetone, and some degenerated, granular casts.

Treatment consisted of peritoneal lavage and parenteral fluid administration. Kidney function returned rapidly after the third day of hospitalization.[3] Before discharge, July 12, 1947, analysis of urine revealed normal findings. A concentration test showed a maximum specific gravity of 1.015, and phenolsulphonthalein test showed 40 per cent excretion. The blood sugar was 114 mg. per 100 c.c.; nonprotein nitrogen, 39 mg. per 100 c.c.; and carbon dioxide, 23.4 meq. per liter. Mantoux test was positive in dilution of 1:10,000. X-rays of the chest and abdomen were normal.

The child was followed in the Pediatric Outpatient Department from August, 1947, to November, 1947. No signs referable to kidney or liver damage were noted. His nonprotein nitrogen on one determination was 36 mg. per 100 c.c. No urines revealed greater concentration than that recorded before his discharge from the hospital. Follow-up chest x-rays showed development of a primary tuberculous complex.

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CASE 2.—D. B. This 2½-year-old white female child was admitted to Denver General Hospital March 7, 1948, approximately forty-five minutes after having ingested one-third cup of home permanent wave neutralizer solution. The child's mother had discovered the accident immediately and had given the child a mixture of raw eggs and milk, which had been vomited promptly. She had repeated this, and the child had repeated emeses prior to her admission to the Emergency Ward at Denver General Hospital, where she received gastric lavage. Past and family histories were noncontributory.

Physical examination at the time of admission revealed an acutely ill, semilethargic, retching white female child with slight abdominal distension. No other abnormal physical findings were apparent. The child was given a hypodermoclysis of 5 per cent glucose in distilled water and allowed to take milk and lactate-Ringer's solution to tolerance every three hours. She retained very little oral fluid and was started on intravenous fluids the following morning and maintained on parenteral fluids for the succeeding forty-eight hours.

During the first forty-eight hours of hospitalization the child was almost anuric, voiding only 70 to 100 c.c. of urine, which was not abnormal except for occasional pus cells, and which had a specific gravity of 1.020. Her initial blood chemistries showed nonprotein nitrogen to be 71 mg. per 100 c.c.; serum carbon dioxide was 17.9 meq. per liter. The mild acidosis was corrected by means of ⅙ molar sodium lactate.

The child's urinary output rapidly increased after the third hospital day. The urine obtained on the fourth hospital day revealed innumerable red blood cells and pus cells. No red blood cells were found in the urine after the seventh hospital day. A culture of urine on the eleventh hospital day revealed the presence of *Escherichia coli*, which rapidly disappeared after treatment with streptomycin.

The child was discharged on the twentieth hospital day. She was readmitted on May 4, 1948, for evaluation of possible kidney damage. Repeated urine analyses, blood chemistries, and an intravenous pyelogram were normal at this time.

CASE 3.—N. C. This 3-year-old white female was admitted to Pediatric Service, Denver General Hospital, Dec. 6, 1948, with a history of having ingested two to three ounces of permanent wave neutralizer solution approximately thirty minutes before admission.

Physical examination at the time of admission revealed no abnormal findings. She was given gastric lavage on admission and 300 c.c. of normal saline solution followed by 500 c.c. 5 per cent glucose in distilled water intravenously. Urine analyses and other laboratory examinations were within normal limits. The child exhibited some vomiting following gastric lavage and appeared slightly lethargic throughout the first thirty-six hours. She voided freely during this time. No other toxic manifestations were seen through the four-day period of hospitalization.

COMMENT

The neutralizer supplied with home permanent wave sets consists of the bromate of either sodium or potassium, more frequently the latter. This is

supplied as a powder which is dissolved in water to make a solution containing 9 Gm. salt per pint of water. If this solution is prepared when the wave solution is applied, then allowed to stand within the reach of small children for hours, it constitutes a hazard. Despite a somewhat bitter taste, solutions left about in teacups are inviting to the run-about child, and in the usual dilution are not sufficiently irritating to the gastric mucosa to cause immediate vomiting.[7]

Little is written regarding the effect of potassium bromate. Experimentally it produces vomiting, diarrhea, central nervous system symptoms (apathy and convulsions), hemolysis, and renal damage. At necropsy dogs who have been subjected to sodium bromate poisoning show hyperemia, bleeding and erosion of the gastric mucosa, and denudation of the esophagus. Renal changes include hyperemia, parenchymal bleeding, and epithelial degeneration which is most marked in the ascending portion of the loop of Henle.[4] Januschke and Inaba[5] report that subcutaneous injections of sodium bromate produce methemoglobinemia in guinea pigs, but this has not been confirmed by other workers.[6] Autopsy material shows severe kidney tubular damage to be a most prominent finding. Necrosis of hepatic cord cells and transverse fragmentation of cardiac muscle fibers are seen.[1]

The three cases reported, together with the fatal cases from the literature,[1, 2] show a range of effects of potassium bromate poisoning in man, varying from gastric irritation without evidence of kidney damage (Case 3), oliguria (Case 2), anuria (Case 1), to fatal termination with toxic nephrosis.[1, 2]

Gastrointestinal effects of potassium bromate depend on the caustic action of hydrobromic acid and free bromine, which are produced by a reaction of bromate and hydrochloric acid in the stomach. The renal damage is due in part to the products of hemolysis and in part to the oxidizing effects of bromate ion of the renal tubules.[4, 6] The first patient showed only a mild degree of anemia, and though no tests for bilirubinemia were made, it is doubtful that hemolysis was an important factor in the production of his anuria.

In the three cases presented central nervous symptoms were not prominent. Some gastrointestinal symptoms were present in all three cases. One child demonstrated no kidney damage while the other two exhibited varying degrees of kidney damage.

The increasing popularity of home permanent waves makes probable an increasing frequency of poisoning with potassium bromate in small children. We have no suggestions for treatment other than that it should be symptomatic and that a mild reducing agent such as activated charcoal or dilute sodium thiosulfate solution should be used in performing gastric lavage. Bromate ions are rapidly reduced after absorption,[7] and a test for bromate is of no value in determining the toxic agent; however, low levels of bromide do appear in the blood stream, and may be of confirmatory value in establishing a diagnosis. Although no bromide determinations were made on the three patients reported, we have recently seen a fourth patient who, following ingestion of approximately two ounces of cold wave neutralizer solution, showed a blood bromide level of 75 mg. per 100 c.c. The course of this 8-year-old boy was almost identical with that reported for the third patient.

SUMMARY

1. Three cases of poisoning due to ingestion of potassium bromate are presented.

2. These cases illustrate a range of effects of toxic action of potassium bromate, varying from moderate gastrointestinal irritation to severe toxic nephrosis.

3. A review of experimental data on the effects of potassium and sodium bromate is presented.

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FEEDING PREMATURE INFANTS

Comparison Of Four Groups Of Premature Infants Fed Different Milk Mixtures

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EVER since the emergence of pediatrics as a specialty, human breast milk has been considered the sine qua non for feeding premature babies. Investigations in the past few years, however, have thrown doubt on the unquestioned supremacy of mother's milk in this field.[1-3] It was thought that further work comparing the growth and well-being of premature babies fed human breast milk with those fed various cow's milk mixtures would be valuable.

It is recognized that premature infants do not handle cow's milk fat as well as some other fats.[4-6] For this reason mixtures low in butter fat content or those in which cow's milk fat was supplanted by olive oil, corn oil, and other fats were used. Also, since premature infants are known to have low serum proteins for the first few months of life,[7] it is generally believed that prematures do better when higher protein feedings are used than are obtained in human breast milk.

MATERIAL

From Sept. 1, 1947, to Aug. 31, 1948, there were 192 premature infants born at the Louisville General Hospital. Of these, ninety-one were not suitable for our study because they either survived less than forty-eight hours or were hospitalized for too short a time to make a study profitable. The remaining 101 babies comprised the material for our study. These infants were, at birth, assigned in rotation to one of four groups, A, B, C, or D. Infants weighing less than 1,750 Gm. at birth were assigned in a separate rotation so that all groups would have a comparable number of small infants.

Group A consisted of thirty infants; twenty-four weighed more than 1,750 Gm. at birth and six weighed less than 1,750 Gm. All of these babies received a mixture of three parts human breast milk to one part of skimmed lactic acid milk. This feeding contained approximately 6.5 per cent carbohydrate, 2.8 per cent fat, and 2 per cent protein, and had a caloric value of approximately 0.61 Calorie per cubic centimeter (see Table I).

Group B consisted of twenty-six infants; twenty weighed more than 1,750 Gm. at birth and six weighed less than 1,750 Gm. These infants received a powdered, modified cow's milk preparation (Similac*), in which part of the cow's milk fat was replaced by olive, coconut, and corn oil. This feeding contained approximately 6.8 per cent carbohydrate, 3.4 per cent fat, and 1.5 per cent protein, and had a caloric value of 0.7 Calorie per cubic centimeter.

Group C consisted of twenty-two infants; sixteen weighed more than 1,750 Gm. at birth and six weighed less than 1,750 Gm. This group received a feed-

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ing mixture of the powdered, modified cow's milk, as described above (Similac*), with added casein hydrolysate (Protolysate†). This mixture contained approximately 6.8 per cent carbohydrate, 3.4 per cent fat, and 5.5 per cent protein, and had a caloric value of approximately 0.86 Calorie per cubic centimeter.

TABLE I. PREPARATION AND COMPOSITION OF FEEDINGS USED

GROUP	METHOD OF PREPARATION OF EACH 100 C.C.		APPROXIMATE PERCENTAGES: CARBOHYDRATE	FAT	PROTEIN	CALORIC VALUE PER C.C.	% CALORIES DERIVED FROM EACH COMPONENT	
A	Breast milk	75 c.c.	6.5	2.8	2.0	0.61	Carbohydrate	44.1
	Skimmed lactic acid milk	25 c.c.					Fat	42.5
							Protein	13.4
B	Powdered modified cow's milk	12.5 Gm.	6.8	3.4	1.5	0.70	Carbohydrate	42.6
	Water to make	100 c.c.					Fat	48.0
							Protein	9.4
C	Powdered modified cow's milk	12.5 Gm.	6.8	3.4	5.5	0.86	Carbohydrate	34.2
	Casein hydrolysate	4.0 Gm.					Fat	38.3
	Water to make	100 c.c.					Protein	27.5
D	Powdered half skimmed cow's milk	14.2 Gm.	5.8	1.5	4.1	0.61	Carbohydrate	43.7
	Water to make	100 c.c.					Fat	25.4
							Protein	30.9

Group D consisted of twenty-three infants; fifteen weighed more than 1,750 Gm. at birth and eight weighed less than 1,750 Gm. These infants received a powdered, half-skimmed cow's milk preparation (Alacta‡), which provided approximately 5.8 per cent carbohydrate, 1.5 per cent fat, and 4.1 per cent protein, and had a caloric value of approximately 0.61 Calorie per cubic centimeter.

METHOD

For the first twelve hours of life, sometimes longer in the case of very small infants, all prematures received nothing by mouth. During the next twelve hours all received feedings of 5 per cent glucose solution. For the second twenty-four-hour period dilute feeding mixtures A, B, C, and D were given to the respective groups. Usually after forty-eight hours mixtures A, B, C, and D were given in undiluted form. A three-hour feeding schedule was maintained uniformly. No attempt was made to standardize the caloric intake in terms of body weight. Rather, depending upon each infant's appetite, the least amount of the mixture which would produce a perceptible weight gain, and at the same time satisfy the infant's hunger, was ordered. Feedings were increased by 3 to 5 c.c. per feeding per day only when a baby's hunger or failure to gain weight demanded it. Almost all infants were given feedings by bottle through a soft rubber "premature" nipple. No feedings were forced, but a few infants too weak to nurse were fed by gavage.

*The Similac used in this study was furnished through the courtesy of M and R Dietetic Laboratories, Inc.

†The Protolysate used in this study was furnished through the courtesy of the Mead Johnson Company.

‡The Alacta used in this study was furnished through the courtesy of the Mead Johnson Company.

After the first seven days all infants received daily vitamin supplements of 5,000 U.S.P. units of Vitamin A, 1,000 U.S.P. units of Vitamin D, and 50 mg. of ascorbic acid. At the end of the second week the daily administration of 0.16 Gm. of ferrous sulfate was begun.

Each group of infants received identical routine premature nursing care until discharged from the hospital. All babies weighed at least 2,500 Gm. when dismissed. Some babies whose poor home conditions demanded that we keep them in the hospital for a longer time weighed considerably more.

At the termination of the period of study, the average age when birth weight was regained, the average mean weight gain in grams per kilogram of body weight per day from the eighth to the eighteenth day of life, and the average length of hospital stay were determined for each group and these results were compared.

RESULTS

Results of this study are recorded in detail in Table II.

Deaths.—Five of the 101 infants studied died during their hospital stay. None of the deaths were directly attributable to the type of feeding received. There were no deaths in Group A. One infant in Group B, birth weight 1,176 Gm. died on the thirty-eighth hospital day after a thirty-hour course of fulminant diarrhea of unknown cause. Two infants in Group C died. One, weighing 2,126 Gm. at birth, died on the fifteenth hospital day after a steadily downhill course marked by persistent vomiting. The other death in this group occurred in an infant weighing 1,290 Gm. at birth. Moderate jaundice and macroglossia were the only significant findings prior to death on the seventeenth day. There were two deaths in Group D. One infant, weighing 1,569 Gm. at birth, died of bronchopneumonia on the fortieth hospital day after a stormy course during which vomiting was the outstanding symptom. The second death in this group occurred on the forty-sixth hospital day in an infant weighing 2,268 Gm. at birth. Post-mortem examination revealed an interventricular septal defect, bronchopneumonia, and atelectasis.

Age Birth Weight Regained.—The infants fed the powdered, modified cow's milk preparation, Group B, regained their birth weight more rapidly than did the infants fed the other milk mixtures. An average of 14.7 days was required for these infants to regain their birth weights, as compared to 21.6 days required for the infants fed the human breast milk mixture, Group A; 17.2 days for the infants fed powdered, modified cow's milk with added casein hydrolysate, Group C; and 20.2 days for the infants fed the powdered, half-skimmed cow's milk preparation, Group D. The over-all average length of time required to regain birth weight was 18.7 days. This time is somewhat longer than that reported by other authors.[8, 9]

Daily Weight Gain.—The mean average daily weight gain in grams per kilogram of body weight from the eighth to the eighteenth day for the entire group was 6.5 Gm. Infants in Group A and B were above average in this regard, gaining 7.3 Gm. per kilogram per day and 8.3 Gm. per kilogram per day, respectively. Groups C and D were somewhat less than average, gaining 5.6 Gm.

TABLE II. MATERIAL AND RESULTS

	GROUP A			GROUP B			GROUP C			GROUP D			TOTAL ALL GROUPS		
	BIRTH WEIGHT OVER 1,750 GM.	BIRTH WEIGHT UNDER 1,750 GM.	TOTAL OR AVERAGE OF ENTIRE GROUP	BIRTH WEIGHT OVER 1,750 GM.	BIRTH WEIGHT UNDER 1,750 GM.	TOTAL OR AVERAGE OF ENTIRE GROUP	BIRTH WEIGHT OVER 1,750 GM.	BIRTH WEIGHT UNDER 1,750 GM.	TOTAL OR AVERAGE OF ENTIRE GROUP	BIRTH WEIGHT OVER 1,750 GM.	BIRTH WEIGHT UNDER 1,750 GM.	TOTAL OR AVERAGE OF ENTIRE GROUP	BIRTH WEIGHT OVER 1,750 GM.	BIRTH WEIGHT UNDER 1,750 GM.	TOTAL OR AVERAGE OF ALL GROUPS
Males			15			12			11			9			47
Females			15			14			11			14			54
White			13			10			7			6			36
Colored			17			16			15			17			65
Total number	24	6	30	20	6	26	16	6	22	15	8	23	75	26	101
Average birth weight (Gm.)	2,123	1,536	2,006	2,100	1,467	1,954	2,140	1,518	1,965	2,137	1,529	1,926	2,123	1,514	1,966
Average age when birth weight regained (days)	19.3	24.4	21.6	14.5	15.2	14.7	15.0	22.6	17.2	20.0	20.7	20.2	17.3	21.0	18.7
Average mean weight gain in grams per kilograms per day	7.5	6.3	7.3	7.7	10.4	8.3	7.3	0.7	5.6	3.8	5.6	4.5	6.7	6.1	6.6
Average length of hospital stay in days	32.9	56.0	38.3	30.2	53.2	35.5	26.1	51.5	33.0	35.2	54.0	41.7	30.7	55.8	37.2
Vomiting			1			2			5			3			11
Diarrhea			1			1			4			3			9
Deaths			0		1	1	1	1	2	1	1	2	2	3	5

per kilogram per day and 4.5 Gm. per kilogram per day, respectively. Our results here are not comparable with those of other authors, since we used for study a period a little earlier in life than is usually used. We did this, however, to enable us to study a number of infants who otherwise could not have been included.

Hospital Stay.—The average length of hospital stay was shortest, thirty-three days, for the group of infants fed powdered, modified cow's milk with added casein hydrolysate, Group C, and was longest, 41.7 days, for the group fed half-skimmed cow's milk, Group D. The group fed the human breast milk plus skimmed lactic acid milk mixture, Group A, had an average hospital stay of 38.3 days, while the group fed powdered, modified cow's milk alone, Group B, remained in the hospital an average of 35.5 days. These periods of hospitalization are a little longer than those reported by various authors as quoted by Wallace, Baumgartner, and Park.[10]

Complications.—Vomiting sufficiently severe to mention occurred in one infant in Group A, two in Group B, five in Group C, and three in Group D. Diarrhea of more than one day's duration occurred in one infant in Group A, one in Group B, four in Group C, and three in Group D.

COMMENTS

To evaluate the results of this study one must bear in mind the fact that these premature babies were not given isocaloric amounts of the various feedings used. On the contrary, a modified self-demand regime permitted each baby to take or refuse whatever amount he chose. Therefore, our results indicate not only the possible advantages of one feeding mixture over another in terms of composition and nutritional efficiency, but also compare some of the ill-defined, but quite important qualities such as acceptability. For example, even though the infants in Group C had the shortest hospital stay, the length of time required for these infants to regain their birth weight and the mean average daily weight gain in the early days were less than for those infants in Group B, because it was found that the very young prematures more readily accepted mixture B, whereas they often refused considerable amounts of mixture C until they were several weeks of age.

The differences noted in the various groups in our study are probably of some statistical significance, but are of far less practical significance. For example, it is impossible to determine by examination at the time of dismissal which infants had any one of the various feedings. Further, it does not necessarily follow that the more rapidly growing babies are the better babies. Lastly, in a study of this nature, it is extremely difficult to say just what part the feeding variations had to play in producing the statistical differences noted.

We do not intend to imply, as a result of the study of such a small number of prematures, that all premature babies should be fed on a modified self-demand basis, nor that any one of the milk mixtures used in this study is necessarily ideal for feeding premature infants. More important is the realization that, given an adequate physical set-up and a trained and interested

nursing staff, practically all of the currently used human breast milk mixtures, as well as cow's milk mixtures, different as they may be in composition and caloric value, accomplish the prime purpose of safely bringing an infant from the stage of prematurity to a level of relative maturity without nutritional deficiency. The speed with which this is done may vary depending upon the feeding used, and often speed is important in terms of reducing the cost of hospital care. Bear in mind, however, the fact that the premature infant himself is not at all interested in the rapidity with which the steps in his development are accomplished. So, although we may at times hurry the premature's course, it is just possible that a happier, equally healthy baby may attain his relative maturity if allowed to proceed at his own rate of growth on a feeding mixture that he readily accepts.

CONCLUSIONS

1. Premature infants do as well or better when fed cow's milk preparations as when fed human breast milk mixtures.

2. Differences noted in the group studied may be more apparent than real and may not necessarily be due to the differences in the feedings given.

SUMMARY

1. A group of 101 premature infants born at Louisville General Hospital from Sept. 1, 1947, to Aug. 31, 1948, were assigned in rotation to one of four groups. Each group received a different milk mixture. All of these infants were fed on a modified self-demand basis.

2. Determinations of the average age when birth weight was regained, the average mean weight gain in grams per kilogram of body weight per day from the eighth to the eighteenth day, and the average length of hospital stay were made for each group at the termination of the period of study.

3. The results were then compared and briefly discussed.

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PYLORIC STENOSIS IN ONE OF IDENTICAL TWINS

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THERE has been discussion and speculation in the literature over the cause of congenital pyloric stenosis. Sheldon[1] was the first to show that when twins are involved, both will be affected if they are uniovular and only one will most likely be affected if they are binovular. This fact, along with the much higher incidence in the male, would suggest a prenatal, possibly a genetic, cause. The following report of a case in which the pyloric stenosis occurred in only one of Negro monozygous twin girls is contrary to what one would expect, and its rarity and implications are worthy of discussion. This is the first reported occurrence of pyloric stenosis in one of monozygotic twins in this country.

CASE REPORT

Twin Negro girls were born at the University of Kansas Medical Center May 1, 1947. The mother, aged 28, was gravida 3, para 2. Her blood Wassermann was 4 plus at the time of delivery, although she had received adequate antisyphilitic treatment. The cord blood Wassermann tests on the twins were negative. The gestation period was 229 days. The first stage of labor lasted one hour, fifty-seven minutes, while the second stage was eleven minutes for Twin 1 and 3 minutes for Twin 2. Twin 1 weighed 1,680 Gm. and measured 41.5 cm. Twin 2 also weighed 1,680 Gm. and was 42 cm. in length.

The weights of both babies were approximately the same until the fifteenth hospital day, when Twin 1 started gaining faster. Perhaps this could be explained on the basis that Twin 2 developed pustules about the neck and an abscess of the back on the thirteenth hospital day. By the thirtieth hospital day, Twin 1 weighed 2,365 Gm. and Twin 2, 2,280 Gm. Twin 1 began vomiting on the thirty-fourth day. By the thirty-ninth day, Twin 1 had lost to 2,300 Gm. while Twin 2 had reached 2,500 Gm. and was sent home.

The vomiting of Twin 1 became forceful and projectile. Peristaltic waves were observed. A definite, firm tumor about 1.5 cm. in diameter was palpated in the right upper quadrant. In a period of five days, 90 Gm. of weight loss were recorded. No change in the number or character of the stools was observed. On the forty-first hospital day, Twin 1 was operated upon; a pyloric tumor was found and a Rammstedt operation was done. The postoperative course was uneventful and the baby was dismissed on the eighteenth postoperative day weighing 2,675 Gm.

The proof that these girls are monozygotic twins is based on the following facts. The accompanying photograph taken when they were twenty months of age shows their identical appearance. The Department of Pathology reported that the placenta had a single chorion and two amnions. Their fingerprints were alike, but not identical. Jenning[2] states that the fingerprints of identical twins are as similar as those of the right and left hand in a single individual. Hoover[3]

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states that in his experience the general pattern can be similar but it is recognized that there can also be differences. The weights, measurements, growth and development, blood grouping, and teething of the twins were similar, as are recorded in the Table of Comparison.

TABLE OF COMPARISON

	TWIN I	TWIN II
Birth Weight	1,680 Gm.	1,680 Gm.
Birth Height	41.5 cm.	42 cm.
Blood Group	A, Rh+	A, Rh+
First Tooth	6 mo.	6 mo.
Sat Up	4.5 mo.	5 mo.
Stood Alone	10 mo.	11 mo.
Walked	11 mo.	12 mo.
Talked	12 mo.	12 mo.
Weight at 20.5 mo.	23 pounds	22.5 pounds
Height at 20.5 mo.	31 inches	31 inches
Head circumference at 20.5 mo.	46 cm.	46 cm.
Chest circumference at 20.5 mo.	48 cm.	47 cm.
Waist circumference at 20.5 mo.	49 cm.	49 cm.
Number of teeth at 20.5 mo.	12	12

Fig. 1.—Twin 1 (left-hand side of picture) of these identical twins developed pyloric stenosis while Twin 2 did not.

DISCUSSION

There have been three reports in the literature in which pyloric stenosis has been described in only one of identical twins. One identical twin girl reported by Lasch[4] in 1925 died of influenza and was considered to have hypertrophic pyloric stenosis at autopsy. However, a pyloric tumor was not felt during life and according to Sheldon the post-mortem description of the pylorus, as given

by Lasch, was not conclusive enough to establish the diagnosis. Sheldon described identical twin boys in 1938, one of whom started vomiting from birth, was constipated, and failed to gain weight. A tumor was palpated, and at operation the diagnosis of pyloric stenosis was confirmed. Sheldon based his belief that the twins were identical on their similar appearance and the fact that "there was only one placenta without any line of fusion, and one set of membranes." Fingerprints were taken and were not facsimilies. Lewis[5] in 1944 described a set of monozygotic twins, one of whom had obvious pyloric stenosis and was operated upon, while the other twin had no vomiting, no weight loss or stool change, but did have peristaltic waves, delayed emptying time, and a palpable tumor. He believed that both of his identical twin boys had pyloric stenosis, but in one it was asymptomatic.

The three cases cited above plus the one reported here represent the exceptions to the usual findings in identical twins. The characteristic findings have been summarized by Laubscher and Smith,[6] who collected all the reported cases of this syndrome in twins. They found that pyloric stenosis had been reported in both twins in eleven of thirteen sets of monozygotic twins, but in only two of twenty-four sets of binovular twins. The high incidence with which pyloric stenosis has been reported in both members of a set of monozygotic twins suggests that the basis of this syndrome is primarily a genetic one. The fact that an occasional set of uniovular twins is observed in which only one of them has symptoms and signs of pyloric stenosis could be explained by the theory that the tumor is present but remains asymptomatic, as suggested by Lewis. It is generally believed that the tumor is present at or before birth. It has been stated that pyloric stenosis has been observed in stillborn infants.[7] If the tumor is well developed at the time of birth, a latent period varying from one to several weeks elapses during which the tumor remains asymptomatic. Wallgren[8] has shown that during this latent period roentgen studies were normal on those who subsequently developed clear-cut symptoms and findings of pyloric stenosis. His failure to demonstrate a pyloric tumor by x-ray does not preclude the presence of such a tumor during this latent period. If the tumor is present at birth and remains asymptomatic for a variable period in those who subsequently develop the definite clinical picture, it would seem to be within the realm of possibility that the tumor might be present at birth in some infants and never produce symptoms. It is suggested that Twin 2 in the present report belongs to the latter group.

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TETANY IN NEWBORN TWINS COINCIDENT WITH MATERNAL TOXEMIA

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THE purpose of this paper is to describe the occurrence of tetany in newborn binovular twins born of a mother with toxemia of pregnancy.

The earliest mention of tetany in the newborn infant was made by Kehrer in 1913.[1] Interest in this condition lapsed until 1931, when Bass and Karelitz[2] reported three newborn infants with this condition. In two of these the mother's intake of vitamin D was apparently adequate. There soon followed similar case reports by Rothstein and others.[3] Bass[4] reviewed the subject in 1942, emphasizing the importance of adequate therapy and the early diagnosis. According to Bakwin,[5] tetany of the newborn infant is related to the hypoparathyroidism which is physiologic during this age period.

In tetany which follows operative removal of the parathyroids, the serum calcium sinks to a low level and the serum phosphorus rises.[6] Similarly, in tetany of the newborn infant the serum calcium is low and the serum phosphorus is generally high. Studies have shown a drop in the serum calcium and a rise in the phosphorus during the first few days of the neonatal period.[5]

It is hoped that this report may throw additional light on the etiology of tetany of the newborn infant.

CASE REPORT

E. B., a 30-year-old Puerto Rican housewife, was admitted to the Lincoln Hospital on April 13, 1946, with the diagnosis of placenta previa and toxemia of pregnancy, pre-eclampsia, following vaginal bleeding. She was a para ii, gravida iii whose last menstrual period was reported as either July 8 or August 8, 1945; so that she was either one month or two days before her expected date of confinement. There had been one full-term normal child fifteen years earlier and an abortion ten years earlier. Her prenatal diet contained a minimal intake of milk. During the preceding six weeks slight pretibial edema was observed. There had been a weight gain of 20 pounds in the previous two months. She was a dark, thin woman with edematous lower extremities, apparently comfortable although slightly apprehensive. The blood pressure was 146/100. The temperature, pulse, and respiration were normal. The hemoglobin was 72 per cent, the urine showed albumin 2 plus. The Wassermann was negative.

Twins were delivered by cesarean section under ether anesthesia. The patient was in good condition after operation except for a blood pressure of 180/94, which in a period of five days fell to 130/80. The urine was negative by the sixth postoperative day. The patient received the regular toxemia routine, sedation, penicillin, etc. She was discharged on April 22, 1946, in a satisfactory state of health.

On May 9, 1946, she was examined after the twins had developed tetany. She appeared slightly thin and pale, but was asymptomatic. X-ray of the long

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bones was negative. The Kline test was negative, the serum calcium was 13.3 mg. per cent, the serum phosphorus 3.2 mg. per cent.

The binovular twin girls, A. and B., weighed 4 pounds, 7½ ounces, and 5 pounds, 3 ounces, respectively, at birth. They received nothing by mouth for twenty-four hours; then 5 per cent lactose water for eighteen hours, and then a mixture consisting of evaporated milk one part, water two parts, plus 5 per cent sugar in adequate feedings every three hours. On April 22, 25 mg. of ascorbic acid and 10 drops of oleum percomorph were added. Both babies were eating well and gaining weight satisfactorily, when, at 13 days, they both developed muscular twitchings as had been observed a few hours earlier in B. In B. these were mostly rightsided, involving the fingers, eyes, and face. In A. the twitchings were mostly leftsided and involved the fingers, foot, and lower jaw. Gradually these twitchings increased in intensity and spread, becoming generalized in both babies so that by May 1, severe clonic seizures occurred frequently. Although the twitchings were generalized, there continued to be a greater localization on the right side in B. and on the left side in A. At this time both babies looked well. They both had moderately thick, mucoid discharge from the nose and A. had a temperature of 101° F. The extremities were slightly rigid and any external stimulus such as noise or handling increased the intensity of the twitchings. All reflexes were exaggerated.

A lumbar puncture on A. was completely negative; on B. was traumatic. The serum calcium on A. was 5.8 mg. per cent, the blood sugar was 72 mg. per cent, the total serum protein was 4.8 per cent, and the Wassermann negative. Serum calcium was not done on B. at this time. The blood sugar was 80 mg. per cent.

On the basis of the convulsions and the low serum calcium, a diagnosis of tetany was made and 5 c.c. of calcium gluconate solution was administered intravenously to each of the babies once daily for the next three days. Calcium chloride in doses of 10 grains three times daily and oleum percomorph, 10 drops twice daily, were also given. In addition, 5,000 units of penicillin were given intramuscularly at 3-hour intervals for five days. The response to the intravenous calcium was dramatic; the severe clonic, convulsive seizures ceased at once. Gradually, over a period of three days, the muscular twitchings became less marked, and by May 4 they disappeared completely. Examination was now entirely negative. On May 3, serum calcium of B. was 8.3 mg. per cent. On May 8, bloods showed:

A.: serum calcium, 12.2 mg. per cent; phosphorus, 5.9 mg. per cent.
B.: serum calcium, 12.7 mg. per cent; phosphorus, 6.0 mg. per cent.

On May 11, calcium chloride therapy was discontinued. On May 16, since both babies weighed over 5½ pounds and seemed well, they were discharged on oleum percomorph 10 drops daily and adequate feedings. A blood specimen, taken just before discharge showed the following values:

A.: serum calcium, 5.6 mg. per cent; phosphorus, 7.7 mg. per cent.
B.: serum calcium, 5.6 mg. per cent; phosphorus, 7.1 mg. per cent.

Both babies were again given calcium chloride, 10 grains every four hours, and the oleum percomorph was increased to 20 drops daily. On May 20, examination of both babies was negative. They were asymptomatic and eating well. A blood on A. showed serum calcium 7.6 mg. per cent, phosphorus 6.5 mg. per cent, phosphatase of 8.1 units. On June 5, A. was found ill with bronchopneumonia. Both babies were readmitted to the Lincoln Hospital. Blood on A. showed serum calcium 11.2 mg. per cent and phosphorus 3.8 mg. per cent. A chest x-ray of A. showed a right upper lobe bronchopneumonia.

She responded well to penicillin and sulfadiazine. During this hospital stay, x-rays of long bones of both A. and B. showed slight elevation of the periosteum over both femurs. Both babies were discharged on July 1, in good health. At this time the serum calciums were A., 9.2 mg. per cent; B., 11.0 mg. per cent.

On May 3, 1948, the twins were just over 2 years old. Examination was negative except for a patent anterior fontanel 1 cm. in diameter observed in both. X-rays of skull and long bones of mother and babies were negative. The blood calciums and phosphoruses were normal.

DISCUSSION

These two cases of tetany in newborn binovular twins of a toxemic mother present several interesting aspects:

1. The diagnosis which was made in the twins was "intracranial hemorrhage," which is said to be the most common cause of convulsions and death in premature infants. Peterman[7] records that 122 out of 176 cases of convulsions in infants under one month of age were caused by cerebral hemorrhage. One wonders how many newborn infants who die from "intracranial hemorrhage" would show a hypocalcemia if the blood were examined.*

2. In these twins, tetanic manifestations began after four days of intensive vitamin D prophylaxis and were fully developed after eight days. Eight days of vitamin D in full dosage, did not modify the symptoms of tetany in the twins.

3. Before the onset of tetany, the food intake and the weight gain were above average. Benjamin, Gordon, and Marples[8] report that the premature infant's ability to retain calcium is excellent, and is better from cow's milk than human milk. Paffrath and Massart[9] report an increased mineralization in prematures on a high calcium diet even without added vitamin D. It appears that prematures can absorb and retain large amounts of dietary calcium. A history of low milk intake and, presumably, low calcium content in the prenatal diet was obtained. This may have had an influence on the production of the hypocalcemic state in the twins.

4. It is a striking coincidence that the tetany began at the same time in both twins, and that they both had an acute rhinitis at a time when none of the other infants in the premature nursery were ill.

5. The maternal toxemia of pregnancy merits consideration as a possible etiologic factor. A study of Kehrer's original report on tetany in the newborn infant revealed that, of the six cases described, there were two female infants, both premature, whose mothers had toxemia of pregnancy. One of the cases reported by Rothstein was born of a mother with pre-eclampsia. He mentions the occasional coincidence of neonatal tetany with maternal pre-eclampsia. King[10] reported tetany in a mother complicating toxemia of pregnancy at parturition. She was relieved immediately of the tetany by intravenously administered calcium, and then delivered premature twins weighing 2,840 and 1,843 Gm., one of whom had slight muscular twitchings. The serum

*Editor's note: Hypocalcemia is a not infrequent accompaniment of cerebral injury in the newborn infant. The finding of a low blood calcium, therefore, by no means rules out the possibility of intracranial hemorrhage.

calciums of the babies at birth (taken after the mother received intravenous calcium prior to delivery) showed the following:

Baby 1: serum calcium, 7.0 mg. per cent; phosphorus, 7.1 mg. per cent.

Baby 2: serum calcium, 7.4 mg. per cent; phosphorus, 6.8 mg. per cent.

Mother (antepartum): serum calcium, 6.0 mg. per cent; phosphorus, 8.3 mg. per cent.

The babies received calcium and cod liver oil orally at birth, and thrived. One month later, the serum calcium of the babies was 9.2 mg. per cent. This report is analogous to ours in many respects.

A perusal of the records of Lincoln Hospital contributed some evidence of a correlation between toxemia of pregnancy and tetany of the newborn. During the period 1940-1948, ten cases of hypocalcemic tetany in babies under 2 weeks of age were observed. In two of these the mothers' charts were unavailable. Of the remaining eight babies, six were born of mothers with toxemia of pregnancy. Of the other two, one mother had cardiac decompensation, and the other showed slight albuminuria (at a subsequent pregnancy two years later she had a 2 plus albuminuria). In the last mentioned instance, fetal distress and torsion of the umbilical cord existed at the delivery. In these eight cases of tetany of the newborn infant, toxemia of pregnancy was present in six mothers and there was a suggestion of some kidney pathology in the other two mothers.

Eclampsia, the severest degree of toxemia of pregnancy, has been labeled a disease of theories since no one etiologic theory seems to be appropriate. One feature of similarity between eclampsia and tetany of the newborn infant is the convulsive tendency.

The occurrence of both conditions at the end of pregnancy, when the maternal organism is subjected to the greatest demand for calcium, and the predilection of eclampsia for twin pregnancies should engage our attention. Kidney decompensation is one of the classic features of eclampsia. This factor, in conjunction with the normally decreased renal function of the newborn infant, particularly the premature,[11] might be linked together in the production of the hypocalcemic state. According to Cantarow,[12] some degree of hypocalcemia occurs commonly in advanced renal failure. He ascribes this to hypoproteinemia or hyperphosphatemia or both.

In view of the above, it would appear justifiable to consider the possibility of an etiologic relationship between toxemia of pregnancy and tetany of the newborn infant.

SUMMARY

1. Hypocalcemic tetany in binovular twins of a mother with toxemia of pregnancy is reported.

2. Evidence is presented, including a review of other hospital cases, for a possible etiologic relationship between maternal toxemia of pregnancy and tetany of the newborn infant.

Blood chemical determinations were done by Miss F. Woll.

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PSEUDOPEPTIC ULCER SYNDROMES IN CHILDREN

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AS ALVAREZ[2] pointed out, symptomatology related to disturbances in the function of the upper gastrointestinal tract may be so similar, regardless of the presence or absence of ulcerative lesions, that the term *pseudo-ulcer* is appropriate when no structural lesions are found. However, this term is, perhaps, unfortunate in that it focusses attention on the gastrointestinal tract and fails to indicate the significance of the common symptomatology. The work of Alvarez,[3] Wolff,[14] and others would indicate that emotional factors can disturb the function of the gastrointestinal tract and account for much of the characteristic symptomatology. There is also considerable clinical evidence that there can be a relationship between these factors and ulcer formation. On the basis of all the evidence, every patient with symptomatology referable to the upper gastrointestinal tract should be considered from a psychosomatic point of view rather than on the basis of the presence or absence of ulcerative lesions.

The foregoing has a distinct bearing on the approach to children with gastrointestinal disorders. The danger of focussing on the stomach lies not only in the difficulties of making an accurate diagnosis of peptic ulcer in children, but, even more important, in neglecting the implications of the symptomatology as evidence of emotional disturbance which can seriously impair the development of the child. In reviewing the pediatric literature, it was found that Kennedy (1933)[9] and later Moore (1941)[12] considered emotional factors to be unimportant in ulcer patients. Franklin (1942)[6] discussed a case in which emotional factors were thought to be playing a role. As will be illustrated by the case histories of two patients, if ulceration is found or suspected and the child treated solely on this basis, the emotional problems will be missed or intensified.

Although the diagnosis of "peptic ulcer" in children appears to be receiving increasing attention, the condition must still be considered uncommon. In a review of all reported cases, Guthrie[7] in 1942 came to the conclusion that peptic ulcers are rare but can occur at any age. A review of 47,353 consecutive admissions to St. Louis Children's Hospital (1934 to 1947) disclosed only eight cases in which a final diagnosis of ulcer was made. Two were girls, aged 5 and 7 years, of whom one had a chronic duodenal ulcer proved by x-ray, the other an acute gastric ulcer associated with a glioblastoma multiforme. Six were boys, aged 1, 7, 10, 11, 12, and 14 years. On the one-year-old child the diagnosis was based on the occurrence of hematemesis, but x-ray findings were negative. The 7-year-old had a duodenal ulcer proved by x-ray. The 10-year-old had a gastric ulcer associated with a brain tumor. The 11-year-old had an acute gastric

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perforation associated with acute appendicitis. The 12-year-old had a chronic duodenal ulcer proved by x-ray, as did the 14-year-old boy. Only four of these cases (a girl of 5 years, and three boys aged 7, 12, and 14 years) had the type of lesion so common in adults (about one in 12,000 admissions). The difficulty of establishing the diagnosis has been repeatedly pointed out,[4, 8, 11] and it would appear that x-ray is the best method of doing this,[13] although it, too, offers difficulties.[5]

The following two patients, admitted to St. Louis Children's Hospital with the diagnosis of peptic ulcer, illustrate the difficulties in diagnosis and the complex and complicated situations that are revealed when such cases are approached from a psychosomatic point of view.

CASE 1.—An 11-year-old white boy was admitted in October, 1948, with complaints of intermittent abdominal pain and vomiting with no constant relationship to food over a period of two years. Several months before the onset he had an appendectomy for similar complaints, with temporary relief. At the onset, an x-ray series was reported as revealing a duodenal ulcer the size of a dime, and he was placed on a diet of milk, eggs, and strained baby foods. He continued to have episodes of abdominal pain, was hospitalized twice, and had to be given intravenous fluids because of severe vomiting. A second x-ray series in May, 1948, was reported as indicating that the ulcer had healed. However, following this, the abdominal symptoms became worse and on admission to Children's Hospital he also complained of weakness, shortness of breath, easy fatigability, dizziness, and lightheadedness.

Physical examination and laboratory findings were essentially negative. There was no evidence of bleeding in vomitus or stool. A barium series revealed no evidence of pathology and there was some question of the validity of the original diagnosis on a review of the x-rays taken at that time. On psychological studies he revealed average intelligence but was not functioning at his maximum level, probably because of an emotional disturbance which was revealed on personality tests.

Personality study.—Both parents were seen in addition to the boy, the father once, the mother several times. It was obvious that the emotional atmosphere of the home contained many sources of tension. The father, on the surface, was a hard-working, ambitious, and successful man, "self-made," until it became obvious that he had received considerable help from his wife. When the going was particularly rough he developed some type of illness through which he could receive a great deal of indulgence and support. He was overtly hostile toward the patient, revealing his own feelings about responsibilities by being very critical of his son's ability to accept responsibility and be independent. There was a close parallel between his feeling toward the patient and toward a younger brother. He frankly favored the patient's sister, aged 10 years, but would at times make efforts to give attention to the patient, usually through some type of indulgence. The mother was the peacemaker and superficially stable but she, too, had many emotional difficulties which could be related to her background. She was an only child, never saw her father after the age of 3 years when her parents were divorced, felt that she had been deprived of many things, had to become independent relatively young, suppressed her resentments, and took over more than her share of responsibilities. She was closely attached to her son and overprotective toward both children. Her deep sense of responsibility extended to her mother, who apparently had done very little for her, was in and out of the patient's home, and was a very disturbing influence because of her harshness

toward the children and the later development of a psychotic disturbance. Both parents had chronic rectal difficulties which required surgery. The sister had an emergency appendectomy two weeks before the patient's operation. The mother has been under treatment for essential hypertension.

So far as could be determined, the patient was a wanted child, at least by the mother. However, she received a rectal tear during his birth which led to a long series of rectal operations. When the patient was 7 months old, the mother went to work because the father underwent an elective rectal operation and their finances were limited at that time. While working, the mother unexpectedly became pregnant again, and with the birth of the second child her rectal difficulties increased. As an infant, the patient did not gain weight on breast feeding, was changed to artificial formulas, and became a feeding problem because no formula seemed to work well. He was trained early for bowel and bladder control by his meticulous mother, and in turn became meticulous and perfectionistic. His physical development was within normal limits although he was sickly, had frequent upper respiratory infections, mastoiditis at 3 years, and a tonsillectomy and adenoidectomy at 4 years. He was treated frequently for a chronic postnasal discharge which cleared up almost miraculously on Benadryl and a special eliminative diet just prior to the onset of his present disturbance.

The patient never revealed much evidence of aggressiveness. His outlets were restricted by high standards set by the family, and to these he passively submitted. Although, on the surface, he had "grown-up" attitudes and interests and seemed to be quite independent, he was found to be closely attached to his mother and fearful of his father, at the same time striving to reach the father's expressed ideal of rugged independence. During the summer prior to admission he went to a camp, apparently could not tolerate the separation from his home, and the vomiting became worse. However, in the hospital it was noted that he had much more in the way of symptomatology if his mother supervised his meals. In this way he revealed the typical conflicts found to be so important by Alexander[15] as a background for the development of upper gastrointestinal disorders, viz., a strong need for love and dependency, and a strong need to deny this.

Because the family lived in a distant city, the treatment situation was necessarily abbreviated and aimed primarily at revealing the emotional problems to the family, who could then get help for these in their own community. No restrictions of diet were made in the hospital and the patient lost his gastrointestinal symptoms within a few days. Concomitantly, he made an excellent relationship with the consulting psychiatrist and was able to express his feelings of fear, loneliness, and anger. "Most of my stomach trouble is due to the fact that I get angry." He seemed to get some understanding of the true basis and direction of these feelings, but this was superficial. The mother used her interviews to pour out feelings about the situation at home and the guilt she felt about acting out some of her feelings in the management of her son's life. She accepted the importance of emotional factors and recognized her own need for psychiatric help. The father used his interviews to express anger at the physicians and resentment toward his son. He had little awareness of the role his personality played in the difficulties at home, but was able to accept the fact that emotional problems were present and treatment was indicated.

A follow-up three months after leaving the hospital indicated that there has been no return of symptoms and the patient made a much better school and social adjustment after his return home. However, the situation was still precarious because the mother had not followed up on the plan of treatment, and the father's attitudes had not fundamentally changed.

While it is uncertain if this boy had an ulcer, he does have the constellation of psychogenic factors which are found to be significant in adults who develop peptic ulcers.[1] It is possible that these factors do not operate as forcefully in childhood because of the greater acceptability of dependency wishes in children than our culture allows for adults. However, in this boy's case there was constant pressure to deny dependency by a feared and punitive father, along with very little real gratification from an embittered and insecure mother. As can be readily seen, the diet of strained baby food and other restrictions served to accentuate his conflicts and problems.

CASE 2.—A 10-year-old Negro boy was admitted in September, 1948, with the chief complaint of abdominal pain and vomiting of ten days' duration. He had five similar episodes over a period of two years, lasting seven to ten days, and relieved by food and a home remedy. These were not effective in this attack, a local physician was consulted, and, after an x-ray series, a diagnosis of "peptic ulcer" was made. A series of "hip shots" was started, but after the first he complained of soreness in his hip, the treatment was discontinued, and admission to the hospital sought. There was also a complaint of "cloudy urine" with indefinite relationship to the abdominal complaints.

Physical examination and laboratory findings were essentially negative. There was no evidence of bleeding in vomitus or stool. Gastric analysis revealed no free acid in the fasting specimen and 11° of free acid after histamine. A barium series was reported as indeterminate with one observer describing an area of "prepyloric gastritis." The original films were reexamined and were considered to reveal no evidence of pathology. Psychological studies revealed the patient to be of average intelligence but functioning below this level because of his emotional disturbance. Most of his problems were found to be related to a deep-seated maladjustment and he was unusually preoccupied with eliminative and anal functions.

The patient was initially put on a diet, but his complaints persisted for several days. The hospital course was uneventful except for a barium impaction which had to be removed. He was seen by the psychiatric service during his stay and was discharged to be followed in the psychiatric outpatient department, where he has been seen regularly once a week.

Personality Study.—It was found that this patient's mother had been a patient in the psychiatric clinic in 1945. At that time she complained of tremors, sweating, smothering sensations, dysphagia, and dysphonia. She discontinued treatment after a few interviews and nothing could be learned about her problems at that time. She brought the same defensive attitudes into the treatment situation of the patient, and, although she attends regularly, has contributed very little to our understanding of his problems.

According to the mother, she was born on a farm in Arkansas and had a happy childhood. She moved to St. Louis with her family at the age of 16 years and did housework until her marriage at 21 years. She had four children, the patient being the third, and the husband deserted after the birth of the last. A brother moved in and supported the family until three years ago, when he married and moved away. The maternal grandmother then moved into the home and took care of the children while the mother worked to support them. This was approximately the time that the mother came to the clinic with her anxiety symptoms. An older brother 13 years old apparently has superior abilities and receives considerable attention for these. An older sister also apparently has superior abilities and none of the siblings are considered to have adjustment problems.

Very little is known of his birth or early development. He was breast-fed until 9 months of age, and forcibly weaned. He became a feeding problem, eating irregularly and sparingly. Toilet training was supposedly uneventful and accomplished at 18 months of age. However, there is evidence of chronic constipation and the repeated use of laxatives. At 6 years he started soiling, and this occurred frequently up to the time of admission. He would complain that his stomach hurt, refuse to go to the toilet, and then have a partial bowel movement. Punishment did not affect this. He was always a restless sleeper and has been sleeping with his grandmother. He is a chronic nailbiter.

In treatment sessions it was difficult to get this patient to verbalize his problems. He expressed considerable resentment toward his mother and siblings, feels that he has been deprived, making excessive demands, and becomes enraged when these are not met. He appears to be closest to his grandmother, who seemingly is the only one who accepts him, and submits to her discipline and punishment without evidence of overt hostility. His relationship to the therapist was passive and submissive until recently when he began to express aggressiveness in play activities. His soiling stopped, but he had one short recurrence of abdominal symptoms.

It is obvious that we are dealing with much different personality problems in this boy than the first. The somatic disturbances are more diffuse and involve the lower as well as the upper gastrointestinal tract. The level of personality development is much more immature, and, although some of the conflicts are similar, the problem-solving techniques are different. This boy's problems are more deeply seated and more handicapping from the point of view of personality development. Treatment is handicapped by the attitudes and problems of the mother, but this is to be expected because the boy's problems are undoubtedly closely related to hers.

The course of children with gastrointestinal disturbances has not been sufficiently well followed to predict what kind of problems may develop if the condition is not adequately treated. Alvarez[2] found that few of his "pseudo-ulcer" patients went on to develop ulcers. Also, in a survey of adult peptic ulcer patients, Klein[10] found that their histories do not indicate an unusually high incidence of gastrointestinal difficulties in children. (Such retrospective studies are not too reliable because of unconscious needs for denial of these disturbances and what they mean in the psychic life of the individual.) However, as an indicator of emotional disturbance the presence of symptomatology associated with gastrointestinal dysfunction merits considerable attention, since it may reveal severe personality disorders which can seriously impair the future development of the child.

SUMMARY AND CONCLUSIONS

Similar symptomatology related to upper gastrointestinal disorders may be present with or without associated ulceration. In either instance, emotional factors may be contributing to a greater or less degree and a psychosomatic approach is necessary.

In children, ulceration is uncommon and difficult to diagnose. Treatment should be based, not on the presence or absence of ulceration, but on the total situation in which the gastrointestinal symptoms can be considered as an indicator of emotional problems.

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CONGENITAL INDIFFERENCE TO PAIN

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UNIVERSAL indifference to pain is apparently of congenital origin. Usually during the second or third year the parents notice that the child does not complain, cry, or show any sign of pain when injured, and does not react to blows, falls, cuts, bruises, burns, and even fractures of bones. In spite of this failure to react to pain, the child always identifies correctly any stimulus applied.

Ford and Wilkins[1] in 1938 reported three cases of unusual insensitivity to pain in children. Dearborn[2] mentioned a 54-year-old man who reported that he had never experienced pain at any time during his life except for dull headaches. He had been a professional entertainer on the vaudeville stage and invited spectators to push pins into his body. He had been insensitive to injuries as long as he could remember. He could not recall ever having had any abdominal or visceral pain of any type. The neurological examination was negative. Critchley[3] mentioned a young man who did not feel pain such as is associated with the lancing of a whitlow. He recognized the pain of a pinprick, but said "it is nothing very much." He had never been sensitive to pain.

Kunkle and Chapman[4] described a 25-year-old white male, a corporal in the United States Army Air Force, who had an almost complete insensitivity to pain and attacks of unconsciousness beginning in childhood. The only other sensory defect was a moderate impairment of perception of heat and cold. The threshold for both superficial pain and deep somatic and visceral pain was greatly elevated. Schilder and Stengel[5] described several patients in whom universal insensitiveness to pain was associated with unilateral lesions in the cortex of the left cerebral hemisphere, chiefly in the region of the supramarginal gyrus. Three post-mortem examinations were made. These authors suggested the term "pain asymbolia."

CASE REPORT

O. M., a 7½-year-old white girl, was admitted to the pediatric service of the Morrisania City Hospital on Nov. 3, 1948, for observation. The mother stated that despite an eighteen-month stay in the first grade, the child did not talk to the teacher and would not or could not learn to read or write or to play with the other children. The child urinated and defecated in bed.

Insensitivity to pain was first noted at about 4 years of age. The mother observed that the patient did not cry or complain when she cut, bruised, burned herself, or was spanked. At the age of 6 years the child was admitted to this hospital because of second-degree burns of her right foot, buttocks, and left knee. Further investigation revealed that while the child was left in the bath tub she had turned on the hot water. She sat in the scalding water for thirty minutes without crying or calling for her mother.

The patient was one of twins and was prematurely born at the Morrisania City Hospital on June 15, 1941. She weighed 3 pounds, 5 ounces. They were the first born children in the family. The delivery was normal and spontaneous following eighteen and one-third hours of labor. The only abnormality noted at birth was a pilonidal sinus. The child was noted to have a "lusty cry" at birth and the Moro reflex was present. She sat up at one year and did not walk until 2½ years. During the first eighteen months of life, this child had been admitted to this hospital five times for various ailments, including gastroenteritis, excoriated buttocks, lobar pneumonia, upper respiratory infection, bilateral, acute, purulent, otitis media, and conjunctivitis. During her hospital residences there were repeated notations that the child was emaciated with macerated buttocks from "negligence and improper diaper care." This condition improved rapidly during each successive hospitalization. At the ages of 3 and 4 years, respectively, she had measles and chicken pox.

The family history disclosed that there were three siblings alive and well. The patient's twin had died at 6 months of age of pneumonia. One grandparent had died of tuberculosis and another was hospitalized for the same illness. An aunt was in an institution because of a mental illness. Specific inquiry did not reveal any peculiarities of behavior or known insensitivity to pain in any other member of the family.

The mother stated that while none of her children had been especially planned, she loved them all equally. However, the patient was punished more frequently as a consequence of her enuresis and her poor school work. The child has told her mother that she "would rather be hit" than be presented with "a pencil for writing and coloring." The mother ascribed her child's poor performance in school to "stubbornness." In the street, if she was hit, the patient would not strike other children nor would she cry. At home she was unduly aggressive toward the other children. She had never overtly expressed any resentment against either parent. The mother appeard to be a dull normal individual who married at the age of 16 years. She did not object to having the child sent to a convalescent home for an indefinite period. The father had been unemployed for some time and apparently made no sincere effort to obtain a job. He did not visit the patient at any time during her six-week stay in the hospital.

The child was thin (weight 33 pounds) and undersized (height 42 inches) with coarse hair, alopecia, cracked nails, hypoplastic teeth, many small, excoriated skin lesions from repeated scratching, and several keloid formations. A systolic murmur was heard at the base of the heart.

She was right-handed. The deep tendon and cutaneous reflexes, cranial nerves, and gait were normal. She manifested no objective response to pinprick, pinching of the skin or muscles (even down to the bone), squeezing of the tendo achillis and ulnar nerves, nor to firm pressure over the supraorbital, sternal, mastoid, and suboccipital regions. Penetration of a No. 19 needle deeply into the buttock elicited no response, but when 30 c.c. of plasma was injected (a normal routine prophylactic procedure) she seemed perturbed but did not cry. The corneal reflexes were diminished bilaterally. The ciliospinal reflex

was absent. She showed a normal response when tested with the Richter dermometer and cold pressor test. The horripilatory response was normal. When a test tube of water at 120° F. was momentarily placed in her hand, she identified it as "hot" and recognized a piece of ice placed against her skin as "cold," but she did not withdraw from either stimulus.

Laboratory studies of the peripheral blood, serology, Schick, Dick, and Mantoux tests were all within normal limits. Wassermann test of the blood and the spinal fluid were negative. The cerebrospinal fluid was under normal pressure and showed no cells, normal protein, sugar, chlorides, Mazzini, and colloidal gold readings.

In the Gesell development tests she identified correctly pictures of a "boy, baby, hat, cup, shoe, flag, house, basket, nickel." She showed a definite reticence in handling test materials at first, but when they were placed in her hands, she accurately performed the simpler tests. She could pick up a ball thrown to her with practically no fumbling and could pile ten small blocks one on top of another without having them tumble. When a block fell into her lap she immediately brought her thighs together and picked up the block. She was able to build some moderately complex block formations after a demonstration by the examiner. These tests were interpreted as approximating the pattern of a 3½-year-old child. More specific testing was rather difficult. The examination had to be interspersed with play or she would refrain from talking or responding. She consistently withdrew from further testing if a crayon and paper were presented to her. This response was never overcome satisfactorily.

During her hospital stay, she spoke spontaneously and freely to all the children on the ward and to the nurses, but at times she used "obscene" language. She was overly friendly and manifested a desire for affection. She took an interest in all the events on the ward and ate ravenously. Enuresis was noted only on two occasions. One morning, when her father was supposed to visit her, she complained of a sick feeling in her stomach, regurgitated her breakfast, and ate her lunch poorly. However, after her mother's visit that same afternoon, she ate her supper well. At the time of her discharge from the hospital, six weeks after her admission, there were no changes in the neurological findings. She was happy, her skin lesions were healed, and her general nutritional status was considerably improved.

DISCUSSION

Sensitivity to painful stimuli is present in early infancy but it is not as acute as in later life. As the infant develops, it becomes more sensitive to all painful impressions until in adult life it probably has reached the acme of sensitivity. From this period until middle age, the perceptive powers probably are stationary. Then, as age advances, they again become reduced, until in old age they are once again at a minimum.

The ability to withstand pain varies not only at different ages, but also among races and individuals of the same race. People vary widely in their sensitiveness to pain and even the same individual may react differently under

different circumstances. Behan[6] states that those of a fair and very delicate skin are most susceptible. In them, the pain receptors, because of lack of protection which is given by a thick epidermis, are more exposed and possibly more subject to irritation. They are not only very susceptible to pain but also to cutaneous irritability of any kind.

Diminished or absent pain sensibility may be present during severe emotion such as great joy, anger, and fear. Some people are unconscious of injuries which occur in states of excitement as in fighting or in competitive sports. Insensitivity to pain may be present during arduous mental work which requires intense concentration or thought, and also in states of mental exaltation, such as is exhibited by religious zealots and during manic episodes. In some cases, by sufficient training there seems to be an ability to inhibit pain perception. Others, because of intense will power or some inherent inability to perceive pain, are comparatively insensitive. Under certain circumstances people who have no analgesia may be quite insensitive to pain or injuries which under other circumstances would give rise to intense pain. Ford and Wilkins[1] assume that there are two factors in our normal response to noxious stimuli: (1) pain as a crude sensation and (2) the reaction to pain which under normal conditions is associated with appropriate emotional elements, including fear. If the latter is minimized in any way, we may become quite indifferent to the former. Their patients were able to distinguish between the sharp and blunt end of a pin and recognized slight differences in the temperatures of test tubes. They had no analgesia or loss of sensibility; they were merely indifferent to pain, and this indifference seemed to be relative in the three cases. Not having analgesia, according to these authors, they cannot be suffering from any defect in the sensory pathways of the spinal cord or the peripheral nerves, and the indifference can scarcely be due to a mental defect, as they represent average individuals of unintelligent stock. They ruled out hysteria and their psychiatric study revealed no trends indicating sadism or masochism. In all three cases their indifference to pain was discovered before the age of 3 years. They are inclined to believe that this condition is due to a congenital dysplasia involving the neural mechanisms concerned in the perception of pain, a defect comparable with color blindness, congenital word deafness, or congenital word blindness. The precise nature of this disorder of sensation is obscure. That the defect lies in the peripheral neural apparatus or spinal cord is improbable.

Since the condition seems to be of congenital origin, the possibility of a congenital defect of the nervous system was considered. Head[7] believed that the cerebral cortex is not essential for the appreciation of pain, for the thalamus is capable of subserving such crude sensations. Kunkle and Chapman[4] were of the opinion that the defect was in the perception of pain and that many but not all of the phenomena of reaction to pain were thereby eliminated and that their findings supported the concept that the sensory defect is central rather than in the end organs or the spinal cord. They were of the belief that pain impulses might travel far enough centrally, perhaps to the thalamus, to initiate a blood pressure rise, and then a little further en route might meet an impasse of some

sort which could prevent the subject from recognizing the experience as painful. In brief, they inferred that the sensory defect is at the cerebral or thalamic level.

Whether or not this universal insensitiveness to pain signifies an asymbolia for pain analagous to a sensory aphasia is highly conjectural. Such a hypothetical condition as pain asymbolia would be a form of agnosia. In the agnosias the difficulty lies not in the appreciation of the sensory stimuli but in the interpretation and understanding of the sensation. The mild congenital word blindness which Ford and Wilkins'[1] first patient exhibited might be taken to favor the idea of a lesion in the region of the supramarginal and angular gyri. The significance of Schilder's[5] observations is not entirely clear, for patients suffering from aphasia are not the most suitable subjects for the examination of sensibility, but if we should accept his conclusions that cortical mechanisms lying in the left hemisphere are essential for the normal reaction to pain, we might consider the possibility that deficient development of such mechanisms might result in disregard of pain.

Pain is clearly a mental phenomenon. It is usually an indication that there is some disturbance of body function. There seems to be a relationship between the degree of mentality and susceptibility to pain. The higher the development and the more vivid the imagination, the greater is the susceptibility. The phlegmatic individual is not particularly affected by pain or emotion. All his sensibilities seem dulled. Psychological factors such as suggestion and diversion of attention are of considerable importance in altering the pain threshold. The apparent insensitiveness to pain in certain types of hysteria, in subjects in hypnotic trances, and in the extraordinary stoicism of religious martyrs is well recognized.

Hysteria, when it produces analgesia, is the result of suggestion and most frequently the product of the examination itself. The hysterical patient is likely to give incorrect answers during the examination. The analgesia is likely to appear and disappear from time to time and to be associated with other hysterical manifestations. Although types of hysteria may occur in childhood, the writers have never seen hysterical analgesia prior to 6 years of age. In the cases reported in children, as well as in our case, the lack of any regional distribution of the sensory disturbance, which is so characteristic of the hysterical clinical picture, is especially noteworthy. The lack of this regional localization would seem to deprive the symptom of any specific psychic connotation or of any value as a significant substitutive gratification. Some psychoanalysts have claimed that insensitiveness to pain may be the expression of a sadomasochistic personality. Masochists apparently delight in pain, but these children do not enjoy pain or seek injuries. They are merely indifferent to pain.

In man, pain is not absolutely essential to life or to reasonably good adjustment because other sensations may be substituted to a great degree in providing the necessary warning signals for individuals whose pain sensation is absent. Apparently, the individual can use his other equipment to help him in detecting those dangerous situations that would ordinarily indicate the use of the pain

apparatus. From childhood, we have learned to estimate the intensity of sensations so that stimuli likely to arouse pain can be avoided. The intensity of the pain depends upon the stimulus, the sensitivity of the patient, the irritability of the nerves, and the extent and number of the nerves involved. The stimuli may be of different degrees and strength, and they may be exerted continuously or intermittently. One factor of importance is the persistence with which the attention of the patient is devoted to the pain, to the exclusion of other topics.

It is necessary to differentiate between the perception of pain and the reactions to the experience. The pain threshold is defined by Hardy, Wolff, and Goodell[8] as the amount of stimulus which will just barely produce a painful sensation under given conditions. In their analysis of the pain experience, they concluded that the pain threshold in man is relatively uniform and stable when measured in instructed subjectes and is independent of age, sex, emotional state, and fatigue within the limits of the ability of the subject to maintain an unprejudiced attitude.

SUMMARY AND CONCLUSION

Insensitivity to pain is a rare anomaly and its exact nature is not defined. Examination of sensibility in children is usually difficult, and in infants only the grossest tests are possible. Indifference to pain in children is apparently of congenital origin and they are not really analgesic, hysterical, or masochistic. The diagnosis is based upon their disregard of potentially painful stimuli and upon the absence of true analgesia. Syringomyelia and defects in the spinal cord should always be considered.

Another case of congenital indifference to pain is reported. No associated neurological abnormalities were found. The mechanism of the defect is probably central. There is no indication in our case nor in the other reported cases of a lesion in any specific part of the brain.

The authors are indebted to Dr. Louis H. Barenberg, Director of Pediatrics, for permission to report this case.

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AN EXPERIMENT IN SEX EDUCATION AT A BOYS' SUMMER CAMP

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A MOTION picture film for school children entitled "Human Growth" has been produced recently by the University of Oregon under the auspices of the S. C. Brown Trust, Division of Social Hygiene Education.

The age levels at which the film aims are the prepubertal and early pubertal periods. With a running time of about twenty minutes, the picture portrays a coeducational classroom in which the pupils view a movie explaining the beginnings of human life, the differences between male and female, and the changes that take place from infancy to adulthood. Following a classroom discussion conducted by the teacher, the audience is invited by the teacher to continue with their own discussion. Nationwide interest in this important film was aroused by a laudatory article about it published in a widely circulated picture magazine.[1] It occurred to me that a valuable experiment could be performed by showing this moving picture at Camp Northwood, a private boys' summer camp. I was interested in observing the emotional reaction of the children to a presentation of this "delicate" subject, and the extent of their understanding as evidenced by the type of questions asked after the showing of the picture. Accordingly, the film was shown on July 16, 1948, to two separate groups of approximately twenty boys each, the 11- to 12-year-olds, and the 13- to 15-year-olds. This arbitrary division was made because I felt that the nature of the questions would differ, and I was curious to see how much they would differ.

Announcement at the supper table that an educational film on the human body was to be shown that evening was the only advance notice given. Stenographic notes and wire recordings were taken of the questions and answers in each group of boys.

To the younger group preliminary remarks were made emphasizing that camping experience in its present concept is, among other things, an educational adventure in an environment close to nature. Brief mention of fundamental biologic principles presumably learned in school was followed by a short description of the format of the film. The boys were encouraged to ask questions after the completion of the movie and announcement was made that at that time all adults were to leave the auditorium.

To the older group, a simple, matter-of-fact description of the format of the film was given. It was suggested that the picture and the ensuing discussion period might augment the boys' knowledge of the subject.

The following questions were asked by each group:

THE YOUNGER GROUP

Do the sperm cells and the egg cells combine the same in all animals?

When the tube that connects the baby is cut, wouldn't it hurt the mother?

Does the uterus ever reach its original size?

The picture showed that at about the age of 22 men grow whiskers. How come a dog, when he is about one year old, and even when he is born, has a lot of hair?

What determines the sex of the child?

In the picture, you notice the sperm breaking the egg. Will you explain that?

What causes twins to be born?

My father has black hair, and my mother has blonde hair, and I have blonde hair. How is that?

What are inherited characteristics?

What causes the change of voice?

How come there are the Siamese twins, where two babies are joined together?

What will happen if a son is born and he has one color hair, and then the mother's hair turns gray? What color hair will the next son have?

Why is it that some females cannot have children?

Is it possible to stop the blood from coming out of the vagina? [referring to menstruation].

Is there anything in the male which may be compared to menstruation in the female?

Why is a baby always born? Couldn't it be a fish or something?

What are blue babies?

Why aren't any people born with blue or green hair?

What is hemophilia?

What is a cesarean operation?

Why don't all babies weigh the same?

Where does a baby come out?

How does the male cell enter into the female?

How many cesarean operations can a woman have?

What would happen if the baby is coming out of the mother and the mother gets a disease or something?

When the baby comes through the belly button, it's very small. How can it get out?

Why does the baby come out head first? Is it top heavy?

How does a horse get a baby?

Why is it that children in a family look alike, but not exactly alike?

In breeding, where the farmer helps the male horse and the female horse, suppose the male horse doesn't want to mate?

Why is it that they won't take milk from a cow until it gives birth?

Why are some babies born without part of the body, like missing a foot?

Do doctors take x-rays before the baby is born to see how it is?

If the mother is blind, can the baby be blind?

THE OLDER GROUP

Can you tell before birth if there are going to be twins?

Why, when you are born, do you look like your parents?

What causes a birthmark?

What determines the sex of the baby?

If something should happen to the mother in six months, is there any chance of the baby being saved?

In the case of stillborn children, once the child is dead inside the mother, do the hormones start to contract the uterus right after the child dies or after nine months?

What is the cause of stillbirth?

Why can't there be an abortion after three months?

Does it ever happen that the sperm doesn't reach the egg?

When do the sex glands develop?

During pregnancy, if the mother should have some kind of disease, like measles, will the baby get that disease?

What causes babies to be born one or two months late?

When a woman can't have a child, is it ever the husband's fault?

How can you overcome sterility?

When a mother and a father have different types of blood and they mate, will the baby die? I mean about the Rh factor.

When a baby is born dead, how does it get out?

Is it possible for a mother to have twins that are too big to fit, like the Siamese twins?

When the cord is cut off the baby, is it put back in the mother?

What happens to the baby's waste while it's inside the mother?

How is the sperm manufactured in the male?

Are triplets identical?

COMMENT

The results of the above experiment were gratifying. The boys of both groups accepted the presentation as an educational feature without the slightest bit of smirking or giggling. The questions were seriously asked and the answers attentively followed. As was anticipated, the questions of the older boys were more technical in nature; almost all of them were obstetrical. Interestingly enough, at the beginning these boys were less at ease than the younger group in asking questions, for they "knew all this" before. Very likely, their attitude was due to the fact that for them the acquisition of sex information was also a very personal matter. Once the questions started, however, they continued without interruption.

Frequent, seemingly casual follow-up conversations with various boys during the rest of the summer, aided by the observations of some of the counselors, failed to reveal that undue sexual excitement was aroused by the experiment. No instances were noted of changed activities among the children, nor change in relation between any boys and their campmates or counselors. Without being able to delve into the innermost thoughts of each individual boy, one received the over-all impression, nevertheless, that the children accepted the presentation as a source of specialized information, or a means of correcting misinformation, not as anything much more dramatic.

Those parents who saw the film and eavesdropped from the outside during the question and answer period were enthusiastic and grateful. Undoubtedly, to many of them this presentation to their child of a subject which they previously may have touched but gingerly represented a prop of some sort, a sharing of responsibility, as well as a source of reference for some future discussions at home. Other parents, who subsequently heard about the presentation, later expressed their approval.

It is now generally agreed that the home should be the site of primary responsibility for sex education of the child. Under optimal conditions a well-adjusted parent is intellectually and emotionally prepared to answer the early simple questions with simple, direct answers, the later more complex problems with sympathy and understanding.

Unfortunately, these optimal conditions rarely prevail. Parents of today were the sexually repressed and ill-informed children of another era, when discussion of the physiologic facts of life was taboo in most families. Consequently, most parents today are not emotionally geared to the task of handling for their children this highly personal subject matter, regardless of whether or not they have the facts straight.

I, therefore, strongly feel that, in addition, the school and the summer camp may well assume important secondary roles in the promulgation of proper sex education to children. Certainly, "Human Growth" and other similar films can be integrated in the educational program of children's camps, along with the nature study activities. Introduction to the beginnings of human life may be aided by concomitant utilization of vegetables, flowers, insects, frogs, chickens, hamsters, and rabbits. The similarities and differences between the beginnings of human life and of these lower forms will thus assume their proper significance in the inquiring mind of the growing child.

It is my belief, further, that elementary and secondary schools should use these films in like manner. Here the problem arises as to who shall instruct the students. At a camp the logical preceptor is the camp physician or nurse. But what about the schools? The University of Oregon authorities[2] are strongly committed to the view that the regular classroom teachers should undertake this type of instruction. They feel that "the normal teaching situation" should prevail, in order not to overdramatize a subject which is emotionally charged to begin with. At the present time, the use of the film in the Oregon schools is only just beginning, so that full evaluation of this point of view must be held in abeyance.

My personal feeling is that this subject is so special that children will not be unduly stimulated by someone other than the teacher conducting the class, provided that someone is an emotionally mature physician or nurse, possibly the school's own physician or nurse, a person who understands and sympathizes with children, a person who commands their respect. Even the Oregon authorities are aware of the fact that "there are teachers who are not sufficiently emotionally adjusted or who may not have the technical data to enable them to undertake such teaching." In the eyes of children, on the other hand, the

doctor and the nurse represent medical authority, their answers accurate and objective, their demeanor imperturbable.

I further believe that for the age levels covered in this paper, sex education, whether at camp or in school, should be presented separately to boys and to girls. Otherwise, group discussion, even under the most expert guidance, would fall far short of its greatest possibilities.

CONCLUSION

1. An experiment in sex education at a private boys' summer camp is described, utilizing the moving picture film "Human Growth."

2. A plan is suggested for sex education in summer camps and in schools.

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Case Reports

ROCKY MOUNTAIN SPOTTED FEVER TREATED WITH CHLOROMYCETIN

Report of Two Cases

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CHLOROMYCETIN has been demonstrated to be an effective antibiotic in experimental rickettsial infections.[1, 2] Typhus fever[3] and scrub typhus[4] have been successfully treated with this antibiotic. It has not yet been extensively utilized in Rocky Mountain spotted fever. Pincoffs and associates[5] reported one group of fifteen patients with this condition successfully treated with chloromycetin. In these patients subjective improvement was noticeable on the second day of treatment. In all cases the temperature dropped to normal levels within seventy-six hours after the initial dose, with an average duration of fever of 2.2 days.

Two cases of Rocky Mountain spotted fever have been successfully treated by us with chloromycetin.

Case 1.—J. P., a boy, aged 3 years, was admitted to the St. Louis County Hospital on May 15, 1949, with a complaint of fever and a skin rash. Eight days before admission the parents had removed several ticks from his body. Four days later he became ill with a temperature of 101 to 103° F., and twelve hours later a rash appeared over the trunk and extremities. Several physicians were consulted during the following several days, and penicillin and sulfonamides were given without benefit. His temperature rose to 105° F., and he was admitted to the hospital.

On admission his temperature was 105.4° F., respirations 64, pulse 200. He was acutely ill. A reddish, macular rash was present over the entire body but was most marked on the extremities. Many of the lesions were purpuric. The spleen was palpable 2 cm. below the costal margin. The remainder of the examination was essentially negative. The laboratory work on admission was as follows: white blood cells, 6,100; red blood cells, 3.2 million; hemoglobin, 10.5 Gm.; differential: stab cells, 38; segmented, 33; lymphocytes 27; monocytes, 2. Agglutinations against typhoid, paratyphoid, brucella, Proteus OX19 and OXK were negative. Routine urinalysis was negative. Blood culture was sterile. Stool culture showed no nonlactose fermenting organisms.

The temperature ranged from 104.6 to 97.0° F. and back to 104.6° F. during the eighteen hours before institution of therapy. At the end of this time chloromycetin was begun with 1.0 Gm. initial dose and 0.25 Gm. every three hours afterward. During the following day the temperature rose to 103.6° F. maximum, and on the second day of therapy the maximum temperature was 102.8° F. Sixty hours after the initial dose the temperature became normal, and he remained afebrile during the remainder of his period of hospitalization. Subjective improvement was definitely evident on the second day of therapy, and by the third day there were no subjective complaints and he felt well. The

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skin rash began to fade on the third day of therapy and had almost entirely disappeared seven days after therapy was instituted.

Five days after admission repeat agglutinations revealed a titer of 1:1,280 for both Proteus OX19 and OXK. Chloromycetin was discontinued on the third day after the temperature became normal. He was discharged nine days after admission.

CASE 2.—R. P., aged 5 years, was admitted to St. Louis County Hospital on May 15, 1949, with a complaint of fever and a skin rash. Ticks had been removed from her body eight days previously. Two days following this, she became ill with fever 101 to 103° F. On the following day a reddish skin rash appeared on her trunk, extremities, and later on her face. She was treated with penicillin and sulfonamides but became steadily worse with the rash becoming more intense until her admission to the hospital.

On admission her temperature was 105.4° F., pulse 144, respirations 36. She was acutely ill with a reddish macular rash over the skin of the trunk and face but most marked over the extremities. Many of the areas were hemorrhagic. The remainder of the examination was essentially negative except for a spleen which was palpable 2 to 3 cm. below the costal margin and some injection of the right tympanic membrane. The laboratory work on admission was as follows: white blood cells, 7,100; red blood cells, 2.99 million; hemoglobin, 9 Gm.; differential: juvenile, 3; stab cells, 44; segmented, 43; lymphocytes, 10. Urinalysis was negative except for an albumin of 1 plus. Agglutinations against typhoid, paratyphoid, Brucella, Proteus OX19 and OXK were negative. Blood culture was sterile. Stool culture revealed no nonlactose fermenting organisms.

During the eighteen hours before institution of therapy, the temperature ranged from 104.8 to 98° F. and back to 104.4° F. Chloromycetin was begun at the end of this period, 1.25 Gm. for the initial dose and 0.25 Gm. every three hours afterward. On the following day the temperature rose to a maximum of 103.4° F., on the second day of therapy to 102° F., and on the third day to only 100.6° F. Eighty hours after institution of therapy she became afebrile and remained so for the remainder of her period of hospitalization.

She began to improve subjectively on the second day of therapy, and the rash began to fade on the fourth day. Seven days after therapy was begun the rash had almost disappeared. Two blood transfusions and parenteral fluids were given as supportive measures.

Repeat agglutinations taken five days after admission revealed a titer of 1:1,280 for Proteus OX19 and OXK.

She was discharged nine days after admission.

COMMENT

Two patients with Rocky Mountain spotted fever were treated successfully with chloromycetin. The results were striking and agreed with the results of Pincoffs and associates.[5] Subjective improvement was definite on the second day after institution of therapy. The temperature dropped steadily by lysis, becoming normal in one patient within sixty hours and in the second within eighty hours after the first dose was administered. The skin rash began to fade on the third and fourth days and had almost disappeared at the time of discharge, nine days after admission. No evidence of toxicity to chloromycetin was noted. The initial dose of chloromycetin was calculated on the basis of 60 mg. per kilogram of body weight with 0.25 Gm. administered orally every three hours afterward.

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EXANTHEM SUBITUM (ROSEOLA INFANTUM) COMPLICATED BY PROLONGED CONVULSIONS AND HEMIPLEGIA

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EXANTHEM subitum has been usually considered a disease in which no complications occur. However it is common to have the disease begin with a short convulsion accompanying the initial high fever. Greenthal[1] reported the incidence of convulsions in his series of cases as 6 per cent. Wallfield[2] reported a boy 12 years of age who developed a convulsion followed by signs of encephalitis. On the third day the temperature fell to normal and the typical rash appeared. The encephalitic signs disappeared with no sequelae. Rosenblum[3] in 1945 described the only case of hemiplegia resulting from exanthem subitum thus far reported. This was a 19-month-old girl who had three convulsions; one lasting for two hours. Lethargy and cervical rigidity followed the seizures and a right-sided weakness was noted. The typical rash appeared on the fourth day. The weakness of the left arm and leg cleared up completely in ten weeks.

CASE 1.—P. M. was a 15-month-old girl who had been irritable for three days, when, on Dec. 15, 1947, her temperature rose to 104.3° F. and she had a generalized convulsion lasting for forty-five minutes. She was admitted to the Rochester General Hospital where, four hours later, she had another convulsion lasting thirty minutes, accompanied by a fever of 106.2° F. The next day she remained stuporous, responding only when disturbed. Weakness of the right arm and leg and the right side of the face were noticed at this time. Frequent clonic movements of the right arm and the leg and the right side of the face were present for the next five days. At times generalized convulsions lasting from two to ten minutes occurred. The spinal fluid on December 18 showed 2 cells with a trace of albumin and a negative culture. The blood culture was also negative. The white blood count on admission was 4,800 but rose to 12,000 after a blood transfusion. The nonprotein nitrogen was 26 mg. per cent, blood sugar 122. The temperature dropped to normal on December 18 and a typical exanthem subitum rash developed on the following day, lasting about twenty-four hours. The stupor continued until December 26, then gradually cleared. The weakness of the face and right leg cleared almost entirely in about two months, but the right arm was still weak twelve months later, particularly the muscles of the right hand.

CASE 2.—J. B. was an 18-month-old boy who had a generalized convulsion on March 18, 1948, lasting for nine hours, associated with a temperature of 105.4° F. and minimal respiratory symptoms. He was admitted to the Newark Hospital at Newark, N. Y. where he remained comatose for several days and was found to have a right hemiplegia. Treatment consisted of sodium phenobarbital, sulfadiazine, and penicillin. The temperature dropped to normal after two days. Twelve hours later the body was covered by a fine macular rash.

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He was seen by a neurosurgical consultant who diagnosed encephalitis with right hemiplegia.

Six months later, on May 3, 1948, he was admitted to the Strong Memorial Hospital because of another convulsion of ten minutes' duration associated with a fever of 104° F. and an upper respiratory infection. Normal findings were obtained from a study of the spinal fluid, the subdural fluid, x-rays of the skull, an intravenous pyelogram, an electroencephalogram, and the blood chemistry. Definite weakness of the right arm and right leg was still present.

CASE 3.—L. L. was an 18-month-old girl who had a forty-five minute convulsion and a temperature of 105° F. Chloral hydrate solution was given per rectum. Thirty minutes later she was noted to be completely disoriented although apparently conscious. The eyes were directed to the left. Definite weakness of the right arm and leg were noted.

By the following morning these signs had cleared completely and no further muscular weakness was apparent. The fever continued intermittently for three days and then remained normal. On the fourth day a typical rash was found on the trunk and face.

DISCUSSION

Nearly all physicians who are experienced in the diagnosis of exanthem subitum will agree that this is a common cause of convulsions during the second year of life. The irritability that nearly always accompanies the disease is one of its outstanding features and usually lasts for two or three days after the rash has disappeared. It is quite possible that the causative agent has a selective action on the brain tissues aside from the possible effect of the high temperature that usually accompanies the infection.

SUMMARY

Three cases of exanthem subitum are reported in which each patient developed hemiplegic weakness following prolonged convulsive seizures. It is probable that this complication of the disease may occur more frequently than in usually believed.

The author expresses his thanks to Dr. Curt Falkenheim for permission to use the third case.

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BACILLUS SUBTILIS SEPTICEMIA TREATED WITH PENICILLIN

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ALTHOUGH *Bacillus subtilis* is ordinarily considered nonpathogenic, a survey of the literature of the last twenty-five years revealed approximately twenty-five cases of infection due to this bacillus. In almost every case the infection followed trauma or occurred in a person chronically ill. The reported infections included panophthalmitis, iridocyclitis, pyelonephritis, pneumonia, mastoiditis, meningitis, and septicemia. There were six cases of septicemia, all of which terminated fatally. Kelemen[1] reported a fatal case of pneumonia and sepsis in the Hungarian literature in 1924. In 1925, Sweany and Pinner[2] reported the first case of *B. subtilis* septicemia in the American literature. This was a postmortem diagnosis in a patient with advanced tuberculosis, who at autopsy was found to have *B. subtilis* in the pulmonary lesions and in the heart's blood. Bais,[3] in 1927, discussed the pathogenicity of *B. subtilis* and reported a third case of fatal septicemia due to the organism. Pellegrini[4] and Anghelescu[5] reported deaths due to *B. subtilis* infections in 1934 and 1937, respectively. Hull, Howie, and Bean[6] had a patient with *B. subtilis* pyelonephritis and terminal septicemia in 1937. All of these cases occurred before the widespread clinical use of the sulfonamides and before the advent of the antibiotics. The following case is the only case of *B. subtilis* septicemia reported since sulfonamides, penicillin, and streptomycin have been available. It responded to treatment with penicillin and sulfadiazine.

CASE REPORT

W. W., a white male infant, was delivered by cesarean section at the North Carolina Baptist Hospital on May 7, 1945. The cesarean section was performed because of cephalopelvic disproportion. The infant appeared normal at birth, and weighed 9 pounds, 4 ounces. The neonatal course was uneventful and he was discharged in good condition on the twelfth day of life.

Although the child took an evaporated milk formula fairly well, he was 5 weeks old before he regained his birth weight. At 6 weeks of age he started refusing his formula. Several changes of food failed to improve his appetite and occasionally he had projectile vomiting. When he was 11 weeks old a physician elsewhere diagnosed anemia and pylorospasm. The hemoglobin at that time was 10.5 Gm. The baby was given 125 c.c. whole blood intravenously in the physician's office and was put on phenobarbital 16 mg. three times a day.

One week later, at 12 weeks of age, the child refused to eat, was fretful, became cyanotic, and was readmitted to the North Carolina Baptist Hospital.

On this admission the baby was poorly nourished and acutely ill. The skin turgor was poor, the temperature was 100.4° F., pulse 160, respirations 64, weight 9 pounds, 8 ounces. The anterior fontanel was sunken, the eyes were glazed, and the pupils were constricted. There was a Kussmaul type of respiration. The lungs and heart were normal. The abdomen was flat and soft, the liver being palpable 2 cm. below the right costal margin. The remainder of the physical examination was normal.

The clinical picture of acidosis was confirmed by a carbon-dioxide combining power of 7 volumes per cent. Other admission laboratory data were as

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follows: In the blood, hemoglobin was 12 Gm., red blood cells 4.09 millions, hematocrit 35 volumes per cent, sedimentation rate 14 mm. per hour, white blood cells 27,350 with 71 per cent polymorphonuclears, 26 per cent lymphocytes, and 4 per cent monocytes; urine was yellow, clear, pH 6.0 specific gravity 1.015, trace of albumin, and negative for sugar, while microscopic examination (centrifuged specimen) showed 30 to 50 white blood cells per high power field, a few granular casts, no acetone or diacetic acid; stool was normal; a blood culture grew *B. subtilis* and a urine culture showed the same organism. Stool and throat cultures were not unusual.

Clinical Course.—On admission the acidosis was treated by administration of ⅙ molar sodium lactate. Although the infant seemed slightly improved, after twelve hours of hospitalization the carbon-dioxide combining power was still 7 volumes per cent, the pyuria persisted and there was moderate, irregular, hyperpyrexia up to 101° F. Penicillin and sulfadiazine therapy were instituted and ⅙ molar sodium lactate was given repeatedly in an attempt to correct the acidosis.

Studies suggested that the chronic acidosis was due to failure of the renal tubules to reabsorb sodium bicarbonate, as described by Dr. Alexis Hartmann.[7] This acidosis was corrected by the daily administration of parenteral ⅙ molar lactate and oral molar lactate solution.

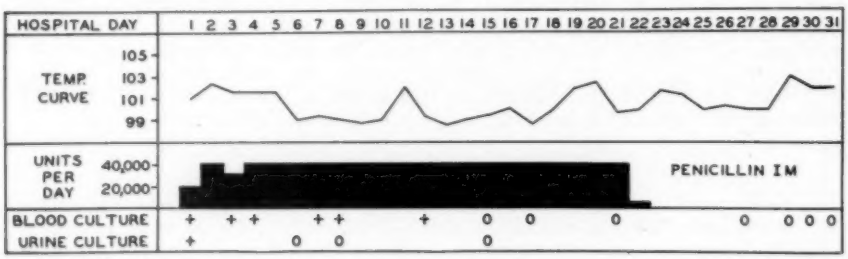

Fig. 1.

When the blood cultures were repeated on the third hospital day they again showed *B. subtilis*, fifteen to twenty colonies per cubic centimeter. It seemed probable that this organism was a contaminant, but five subsequent cultures revealed pure cultures of *B. subtilis* (Fig. 1). Urine cultures were sterile after the first hospital day. When the *B. subtilis* septicemia was fully proved, sulfadiazine was discontinued and penicillin, 40,000 units daily, was continued for twenty-one days. By the fourth hospital day the baby was greatly improved. His carbon-dioxide combining power was still fluctuating but he was alert and was eating well.

On the thirteenth day of penicillin the blood cultures became sterile and remained sterile thereafter. During the course of the septicemia and for a week after the blood cultures were sterile, the pyuria continued and the infant had a low-grade, irregular fever. After the blood stream became sterile the level of the carbon-dioxide combining power became more stable. We credited this partly to the clearing of the infection and partly to more accurate determination of the baby's daily alkali requirement after observation of his response.

At the end of thirty days the patient was afebrile and his general condition was good. His discharge weight was 11 pounds, one ounce. He was discharged on a maintenance dose of molar sodium lactate solution. The baby returned each month for regulation of his dose of molar lactate solution. Blood cultures were drawn on the first two of these monthly visits and these were sterile.

DISCUSSION

The first blood and urine cultures revealed a large, gram-positive rod. Five other blood cultures contained pure growths of the rod but repeated urine cultures were sterile. The large gram-positive rod which was consistently found had the following cultural and chemical characteristics which identified it as a strain of *B. subtilis*. It was an aerobic, spore-forming, gram-positive, motile rod. On pour plates the colonies were irregular, hemolytic, rapidly growing, and after twenty-four hours quite large. The colonies were visible within six hours after inoculation. On transplants to aerobic blood plates they were medium sized, white, wrinkled, and hemolytic. In broth the rod had a heavy growth, forming a scum on the surface. The organism alkalinized litmus milk and liquified gelatin. A 1:1,000 suspension of the organism injected intraperitoneally did not kill a mouse and the spores were not killed by boiling for ten minutes.

Most strains of *B. subtilis* are sensitive to penicillin. In fact, they are so consistently sensitive that this rod has been used in the assay of penicillin.[8] This antibiotic would, therefore, seem ideal for treating infections due to *B. subtilis*. In vitro penicillin sensitivity tests on our organism showed it to be inhibited by a concentration of 0.1 unit per cubic centimeters. Lower concentrations were not tested. The bacillus was also tested against sulfadiazine, sulfathiazole, sulfanilamide, sulfamerazine, and streptomycin. It was not inhibited by concentrations of 12.5 mg. per cent of each of the sulfonamides but streptomycin inhibited the organism in a concentration of 8 units per cubic centimeter.

It is difficult to evaluate the role of the septicemia in this child's illness. We postulate that the baby's earlier difficulties were due to his acidbase imbalance, that the *B. subtilis* was probably introduced by contamination of the blood transfusion given one week prior to hospital admission, and that the infection precipitated the acidotic crisis. The pyuria was felt to be due to infection by *B. subtilis*. There are reports of cases of pyelonephritis proved at autopsy to be due to this organism.[6, 9]

It is interesting to report that the boy's alkali requirement gradually diminished so that at 14 months of age the molar lactate solution could be discontinued. At that age he appeared to be a sturdy, normal boy.

SUMMARY

A case of *B. subtilis* septicemia is presented. The organism was sensitive in vitro to both penicillin and streptomycin in concentrations obtainable in vivo. Treatment with penicillin (815,000 units total dosage) was successful. Penicillin is suggested in the treatment of *B. subtilis* infections.

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VIRGINAL HYPERTROPHY OF THE BREAST

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VARIOUS types of breast enlargement are encountered in pediatric practice from the newborn period through puberty and adolescence. Unilateral or bilateral enlargement frequently occurs in children of either sex and both mammary and adipose tissues may be involved. Bronstein and Cassorla[1] classified the breast enlargements in infancy and childhood in the following groups: (1) newborn type; (2) adolescent type; (3) those with associated endocrinopathies; (4) enlargements artificially induced; and (5) a miscellaneous group. In the latter group, the breast enlargements associated with cirrhosis of the liver, leucemia, testicular atrophy, carcinoma, and the so-called "mastitis gargantuan" are briefly mentioned.

Massive breast hypertrophy in adolescence has been observed occasionally and is apparently an independent entity. This condition has been termed variously as virginal, puberal, massive diffuse, or nongravid hypertrophy. Although cases have been described at a mature age or during pregnancy, the condition is usually observed at puberty, shortly before or after the menarche. Geschickter,[2] in a review of thirty cases of massive hypertrophy, noted that in twenty-four the onset was between 11 and 16 years of age; four others followed pregnancy, and two cases were associated with a menstrual disturbance. Bilateral involvement is most frequent, and the diffuse hypertrophy may eventually give rise to enormous pear-shaped organs.

Ordinarily after onset the enlargement goes on rapidly for a period of several months. The breasts become firm and tense, the superficial veins are dilated, and the areola are enlarged. As the weight of the breast increases it becomes pendulous, and dependent portions may be cyanotic. Pain and tenderness are transient or absent and a dragging sensation and the cosmetic deformity are the chief complaints. Mammary enlargement of considerable size may be associated with superficial ulceration of the skin.

We are reporting a case of unilateral virginal hypertrophy in a girl 12 years of age. The rarity of the condition is indicated by the paucity of reported cases and our inability to find reports of these cases in pediatric literature. This report of a case calls attention to the occasional occurrence of this unusual disorder in adolescent girls. The possibility of severe emotional disturbances in virginal hypertrophy and the radical surgery necessary for correction of the condition deserves special consideration.

CASE REPORT

R. W., a girl aged 12 years, was first seen on April 14, 1948, with the complaint of enlargement of the left breast. The birth history was normal, and the past medical history, except for the occurrence of mumps, chicken pox, rubella, and rubeola in the preschool period, was negative. She had never menstruated. The family history was essentially negative.

The patient's general health had always been excellent. For a month preceding examination she had noted that the left breast was larger than the right, and for at least two weeks discoloration of the breast had been observed.

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Fever, local pain, or tenderness had not occurred, and breast enlargement was the sole concern of the patient and her parents.

On physical examination weight was 114 pounds, height 65½ inches, temperature 98° F., blood pressure 116/70, and pulse 72. She was an alert, attractive, and well-looking child. Examination was essentially negative except that the left breast was enlarged, tense, slightly cyanotic, and the superficial veins were prominent in the upper quadrants. No tenderness or localized masses were noted. The areola appeared enlarged, and the nipple was retracted. There was scant axillary hair, a normal female puberal escutcheon, and the vagina and cervix appeared normal. Upon rectal examination, the uterus was found to be of normal size, and the adnexa were normal. Vaginal smears taken for estrogenic activity showed few mature vaginal epithelial cells with scant glycogen content.

Urinalysis showed a specific gravity of 1.026, acid reaction, and negative albumin, sugar, and microscopic. Blood count showed hemoglobin 14 Gm. per 91 per cent, erythrocytes 4,580,000, leucocytes 7,450, neutrophiles 64 per cent, lymphocytes 35 per cent, and eosinophiles 1 per cent. The blood Kline and Kahn tests were negative, and the sedimentation rate (Smith) showed 0.5 mm. settling in fifteen minutes and 1.5 mm. in forty-five minutes. X-ray of the chest was negative, and x-rays of the wrists showed all ossification centers present except the pisiform; the ulnar epiphysis was open.

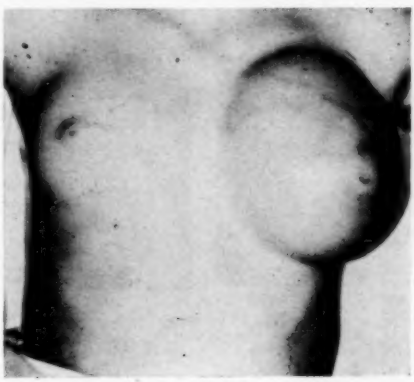

Fig. 1.—Note the slightly pendulous breast with prominent veins in the upper quadrants.

On April 15, 1948, she was hospitalized and a diagnostic aspiration of the breast was done. No blood, pus, or tissue was obtained, and, subsequently a dry dressing was applied and parenteral penicillin administered. Little change in the appearance of the breast was noted, and she was dismissed from the hospital on April 17. Later in April and in early May, three x-ray treatments were given to the breast without change in size or appearance of the breast. The breast increased gradually in size and by June 10, 1948, had become slightly pendulous (Fig. 1). By this time the mother had become most concerned about the progressive breast enlargement and presented a severe emotional problem, although the patient never seemed at all disturbed.

On June 26, 1948, a tentative diagnosis of virginal hypertrophy was made. Under Pentothal Sodium and nitrous oxide anesthesia, a biopsy of left breast tissue was obtained. Specimens were taken from the principal gland mass and

also at the junction of glandular and areolar tissue. On this date the breast appeared uniformly hypertrophic, and the enlargement was not in the form of a discrete tumor mass. Specimens from both sites were grossly firm, elastic, and of a rather homogeneous appearance.

The pathologist's report was:

"There is an abundance of ducts and the acinar structures have not appeared. In the ducts there is a thickening of lining epithelium with an increased number of cells. There is an occasional papillary excrescence with attempts to form secondary lumens. A marked increase in interstitial connective tissue is present, involving both periductal fibroblasts and those lying between the ducts. The fibroblasts appear immature and often pseudomyxomatous. Mitotic figures are present but not common, and in many areas there is deposition of immature collagen. If this specimen had been received from a more mature breast, it would be called a fetal type of fibro-adenoma. The clinical and gross pathological picture suggests virginal hypertrophy, and in this condition fibro-adenomatous growth is not uncommon. Diagnosis: Virginal hypertrophy of left breast with early fibro-adenomatous changes." (Fig. 2.)

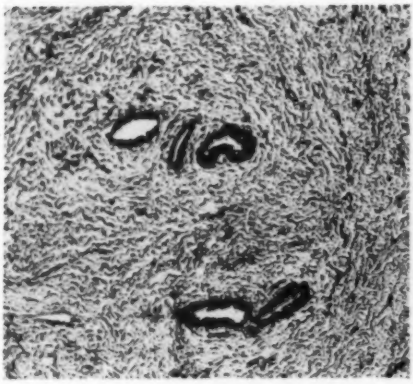

Fig. 2.

Fig. 3.

Fig. 2.—The thickening of the lining of the ducts and the marked increase in interstitial connective tissue is prominent.

Fig. 3.—Photograph four months postoperatively.

On June 28, under Pentothal Sodium and nitrous oxide anesthesia, a simple mastectomy was done. The postoperative course was uneventful, and she was dismissed from the hospital six days following the surgical procedure.

The gross specimen (left breast) weighed 1,350 grams. Section of a surface showed a firm, rubbery, homogeneous glandular tissue of pinkish color. Microscopic findings were similar in all detail to the biopsy specimen.

She has been seen on several occasions since surgery. On the last visit, Nov. 6, 1948, she was perfectly well, normally active, and emotionally stable. The scar on the left chest was satisfactory (Fig. 3). Physical examination was essentially negative, and menstruation had not occurred at that time. In a letter from the mother, menstruation was reported to have started in December, 1948.

COMMENT

The cause of virginal hypertrophy is obscure. Schauffler[3] has called attention to the fact that general hormonologic backgrounds in relation to the

breast are vague. Estrogen appears to stimulate the growth of duct epithelium, whereas progestin affects the development of the alveolae during pregnancy. A rather obscure factor, now differentiated from the anterior pituitary, and called "mammogen" supposedly stimulates the growth of the entire breast. Harris and Rosenthal[4] considered a hormonal imbalance or continued stimulation by estrogenic substances as a possible cause of virginal hypertrophy. Certainly in this condition physiologic puerperal hyperplasia is not involved, and, therefore, the lactogenic hormone is not concerned in the process. Fisher[5] and associates noted the possible unfavorable effects in treatment of a patient by administration of female sex hormones; during treatment the breasts increased in size. Gaines[6] stated that the weight of evidence points to a conclusion that virginal hypertrophy is an exaggeration of normal growth seen at puberty with direct stimulus by estrogenic and possibly also the corpus luteum hormone. Abnormal sensitivity on the part of the end organ to hormonal stimuli is indicated also in those cases in which the enlargement is unilateral.

Geschickter has described the pathology of the hypertrophied breast as an exaggeration of normal adolescent development. The growth consists of an extension of ducts with marked increase in the periductal and interlobular connective tissue. Lobule formation may occur and mammary ducts show increase in size and number of their lining cells with moderate surrounding lymphocytic infiltration. The ducts are moderately dilated, but in the later stages a preponderance of sclerotic and hyalinized connective tissue compresses the ducts and leads to atrophy of many of the branches. Diffuse virginal hypertrophy may be accompanied by localized fibroadenoma, and the subsequent development of cancer and abscess formation has been reported.

In this patient, enormous breast enlargement (mastitis gargantuan) was not observed since surgical amputation was undertaken in a relatively early period. The rate of enlargement was not unusual since the period of most rapid growth is usually during the first three to four months. It would seem preferable to perform mastectomy or plastic surgery of the breast before the tremendous enlargement occurs, thus sparing these young patients the marked psychic and physical changes which may ensue. A plastic procedure was not feasible in this case since the entire breast was diffusely involved. At no time during observation of our case, either before or after surgery, was the patient disturbed, self-conscious, or apprehensive. The condition, however, became an obsession with the mother, and prior to surgery she demonstrated emotional disturbances and unusual anxiety. Such exaggerated emphasis on the enlargement by the mother over a longer period of time might have caused considerable harm. The unilateral enlargement and the occurrence prior to the menarche have been observed infrequently.

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THE FULMINANT FORM OF EPIDEMIC HEPATITIS IN A TWO-MONTH-OLD INFANT

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TO OUR knowledge the following case is the first reported instance of the fulminant form of epidemic hepatitis occurring in an infant.

In a recent paper Lucké and Mallory[1] described the fulminant form of epidemic hepatitis. This form of the disease in adults is characterized clinically by intense severity of symptoms and death within ten days of onset. Pathologically, the distinctive findings are severe uniform autolytic necrosis of liver cells accompanied by an intensive inflammatory reaction with regenerative hyperplasia of the bile duct epithelium.

CASE REPORT

An 8-week-old male infant of Italian and German descent was admitted to the Fort Hamilton Station Hospital, N. Y., because of jaundice.

Five days before admission it was noted that his urine had become orange in color. This was accompanied by increasing yellow discoloration of the skin and paleness of the stools. No fever was noted and neither gastrointestinal nor respiratory symptoms were apparent.

The patient was the third sibling, born at term with no apparent abnormalities, weighing 5 pounds, 8 ounces. There was no family history of anemia or jaundice.

Two weeks before the onset of this illness there had been a three-day episode of diarrhea which responded to dietary measures.

Three weeks prior to the onset of jaundice, he had been cared for by a 20-year-old girl who had an upper respiratory infection.

On admission he was well-developed and weighed 8½ pounds. The skin was moderately dry and jaundiced. The conjunctivae and buccal membranes were tinged yellow. The liver edge was palpated three fingerbreadths below the right costal margin, and the spleen almost an equal distance below the left costal margin. Temperature, pulse, and respirations were normal. The remainder of the examination was not remarkable. He was fed a standard formula which he took well and retained.

On the morning of the second hospital day he vomited a few ounces of coffee-ground material. The urine was dark yellow. Other than moderate lethargy, there were no further physical findings. By afternoon the temperature had risen to 100.2° F., lethargy had increased noticeably, and the jaundice was intensified. The erythrocyte count was 3.64 million per cubic millimeter with 11.5 Gm. per cent of hemoglobin and a hematocrit of 27 per cent. The leucocyte count was 15,400 per cubic millimeter with 61 per cent lymphocytes, 34 per cent neutrophiles, 4 per cent monocytes, and 1 per cent eosinophiles. Urinalysis revealed 1 plus albumin, 1 plus sugar, a positive reaction for bile with nitric acid, a trace of acetone, and 8 to 10 pus cells per high-power field. The icteric index was 78 and the immediate direct Van den Bergh reaction was positive with 0.937 mg. per cent of bilirubin in the serum. The blood Wassermann was positive and the blood Kahn was doubtful. The blood type was 0, Rh positive.

During the second night of hospitalization the infant vomited repeatedly. By early morning the temperature was 97° F. and the patient suffered a clonic convulsion of the left arm and leg lasting for eighteen minutes. Following this

*Pathology Section, First Army Area Medical Laboratory.
†Pediatric Section, Fort Hamilton Station Hospital.

the respirations were rapid and labored. Coarse râles were heard throughout both lungs. The liver and spleen had decreased in size. Mild nuchal rigidity was present and the knee jerks were hyperactive. Sustained ankle clonus was elicited. Lumbar puncture showed nothing of note in dynamics, cytology, or chemistry. Oxygen and penicillin were administered, three hundred cubic centimeters of 5 per cent dextrose in distilled water, followed by 80 c.c. of whole blood were given by venoclysis. The cephalin flocculation test was reported 4 plus after twenty-four and forty-eight hours.

The clinical course deteriorated progressively. Cyanosis occurred despite oxygen. The perineum and buttocks became edematous and the patient expired on the evening of the fourth hospital day, which was the ninth day after onset of symptoms.

POST-MORTEM EXAMINATION

Complete necropsy was performed twelve hours after death. The body weight was 3,800 Gm. Development was consistent with the age of 2 months. The state of nutrition was good. The sclerae and skin were orange-green. The perineum and buttocks were moderately edematous. The pleural and peritoneal linings were orange-green, glistening, smooth, and their cavities contained no fluid. The pertinent gross changes were found in the lungs, spleen, liver and kidneys.

The lungs together weighed 85 grams. They were purple and firm, particularly in their dependent portions. The cut surfaces exuded bloody fluid.

The spleen weighed 14 grams and was softened. The sectioned surfaces were moist with blood but not diffluent.

The liver weighed 99 grams, appeared to be shrunken, and was of uniform, rubbery consistency. Its external surface was smooth, patchy pink and tan. The lower edge was sharp.

The entire bile duct system appeared normal. The sectioned surface presented a nutmeg mottled pattern of pink and tan with uniform greenish tinge of minimal degree.

The kidneys were softened, their combined weight being 36 grams. They were otherwise not unusual.

MICROSCOPIC EXAMINATION*

Histopathologic findings other than those within the lungs, spleen, liver, and kidneys were not pertinent.

The lung sections showed scattered emphysema, congestion, hemorrhage, and edema. Phagocytes were numerous within the alveoli. These were unusual in that their cytoplasm contained foamy and vacuolar spaces which were identified as fat on Sudan IV stained sections. The fat droplets were generally smaller than the nucleus. No free fat or foreign material was present within the alveolar spaces.

The spleen contained diffusely enlarged malpighian follicles. Their germinal centers were widened and showed mild phagocytosis with polymorphonuclear leucocyte infiltration. The sinusoids were congested and contained moderately numerous neutrophiles, eosinophiles, and phagocytes. Erythropoietic foci were not present.

Striking changes were found within the liver (Figs. 1, 2, and 3). The parenchymal cells had undergone uniform and almost complete autolytic necrosis. A few remaining parenchymal cells could be identified singly and in groups. These were most numerous at the lobular margins and showed severe vacuolar and granular degeneration of cytoplasm with pyknosis and lysis of their nuclei. Regenerating liver cells could not be found. Many histiocytes and small amounts of cellular debris filled the inter-reticular meshes ordinarily occupied by paren-

*The histopathologic diagnosis in this case was concurred by the staff of the Army Institute of Pathology.

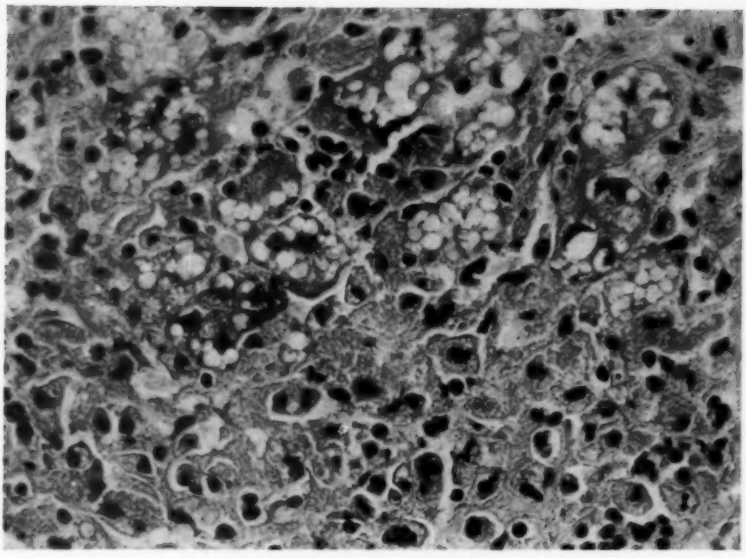

Fig. 1.—Liver, showing autolytic necrosis of hepatic cells with infiltration by histiocytes and inflammatory cells. Vacuolar degeneration of cytoplasm and karyolysis of nuclei are seen in the remaining hepatic cells.

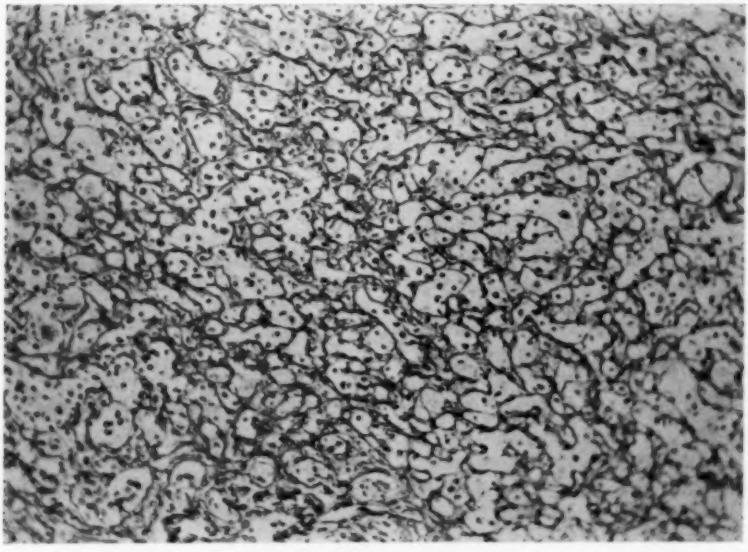

Fig. 2.—Liver, showing preservation of reticulum throughout lobule. Wilder reticulum stain.

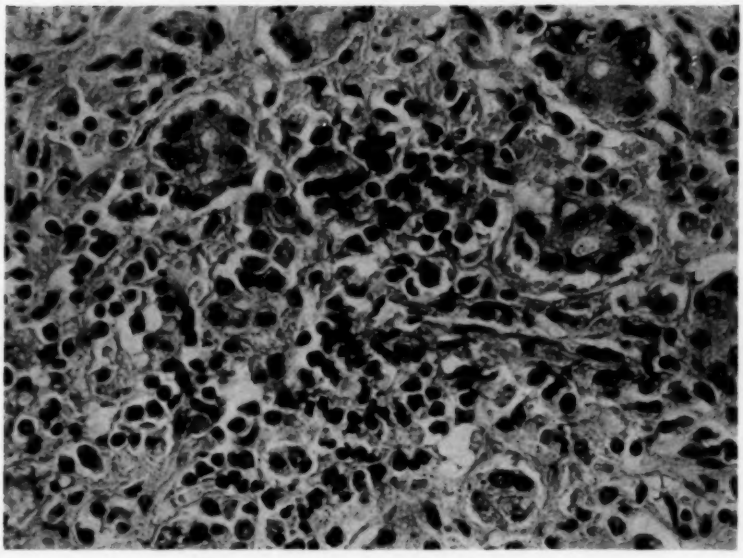

Fig. 3.—Liver, showing regenerative hyperplasia of bile ducts with polymorphous infiltration of inflammatory cells; most dense in the portal space.

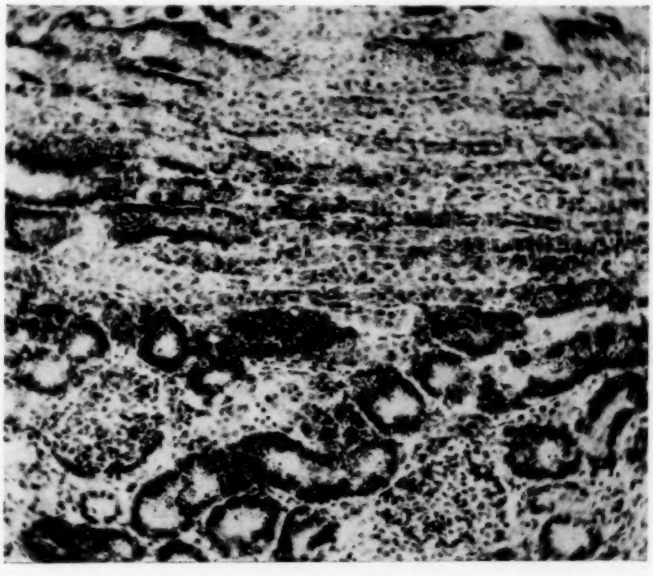

Fig. 4.—Kidney, showing infiltration of tubular epithelium by sudanophilic droplets. Sudan IV stain.

chymal cells. Lymphocytes, plasma cells, neutrophiles, and eosinophiles were present throughout the liver. These inflammatory cells were most numerous in the periphery of the lobules, the perilobular stroma, and interlobular stroma. The reticulum structure of the liver was not altered in sections stained by Wilder's method (Fig. 2). Endophlebitis was not observed. Many irregular twigs of regenerating bile duct epithelium were present within the perilobular and interlobular stroma (Fig. 3).

The kidneys also presented unusual histologic findings (Fig. 4). The capsular spaces contained a small amount of albuminous precipitate, the glomeruli being otherwise unaltered. The lining cells of the proximal convoluted tubules were swollen. Within their cytoplasm were numerous foamy and vacuolar clear spaces which were small and concentrated within the basal portion of the cell. On Sudan IV stained sections they were found to contain fat. Smaller numbers of similar vacuoles were found within the epithelium of the loops of Henle, distal convoluted tubules, and collecting tubules. Sudanophilic droplets were present within the tubular lumens throughout the entire nephron. The number of fat droplets diminished gradually toward the distal portions of the tubules. Neither necrosis nor severe degenerative change was observed within the tubules.

DISCUSSION

The manner in which the infectious agent was acquired could not be determined in this case. The positive Kahn and Wassermann reactions were believed to be false, as evidence of syphilis was not found in either parent or in the infant.

Terminal neurologic findings, respiratory failure and edema of the buttocks and perineum as seen in this case were described by Lucké and Mallory in their adult cases of the fulminant form of epidemic hepatitis.[1]

Epidemic hepatitis is of unusual occurrence in infants less than one year of age.[2, 3, 4] Many cases are described in the 1- to 5-year age group.[5, 6, 7] The course of the disease in infants and children is usually milder and of shorter duration than in adults. This point was emphasized by Horstmann and associates in a study of two epidemics.[5]

No pathologically proved cases of epidemic hepatitis terminating in death have been recorded in infants heretofore. In 1927 M. T. Morgan and H. C. Brown reported a pathologically examined case in an 11-year-old child which terminated fatally in nine days.[8] This is the youngest proved case of the fulminant form of epidemic hepatitis which was found in a survey of the literature.

CONCLUSION

A case of the fulminant form of epidemic hepatitis has been described in an 8-week-old infant. This is believed to be the first recorded instance of this form of the disease in an infant.

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Clinical Conference

WEEKLY DIAGNOSTIC CONFERENCE IN PEDIATRICS, AT THE CHARITY HOSPITAL OF LOUISIANA AT NEW ORLEANS

THIS CONFERENCE IS HELD EACH FRIDAY AT NOON, JOINTLY BY THE THREE PEDIATRIC DIVISIONS: LOUISIANA STATE UNIVERSITY MEDICAL SCHOOL, DR. MYRON E. WEGMAN, PROFESSOR; TULANE MEDICAL SCHOOL, DR. RALPH V. PLATOU, PROFESSOR; AND INDEPENDENT SERVICE, DR. ALMA SULLIVAN, IN CHARGE

DR. JOSEPH CRAVEN (Resident, Independent Division).—Are there any follow-up reports from last week?

DR. ROY A. KELLY (Resident, Louisiana State University Division).—You will recall the 9-year-old child we discussed at some length here two weeks ago, who appeared so well despite the presence of a suppurative lesion in the upper lobe of his right lung. Though the tuberculin reaction had been positive, we found no other evidence of tuberculous etiology. Lobectomy was done on the day following, and the boy has had a very smooth convalescence; our pathologists reported multiple abscesses and a mixed bacterial flora, but no evidence of tuberculosis.

DR. H. TOLMAS (Resident, Independent Division).—All the diagnostic procedures that were suggested for the 2-year-old Negro boy with apparent glycogen storage disease appeared to be confirmatory. We are now studying galactose and levulose tolerance tests with the hope that they will be helpful in guiding further management.

DR. WILLIAM NEWSOM (Resident, Tulane Division).—The very striking example of unexplained subcutaneous fat necrosis which had spread gradually to involve almost the entire back of an otherwise apparently healthy newborn infant has now cleared almost completely during the past six weeks. A biopsy confirmed our clinical impression.

Case 1. Congenital Syphilis

DR. GEORGE PRATHER (Resident, Tulane Division).—This is a white female infant who was born at home after an uneventful pregnancy; no complications were noted by the physician at the time of delivery. The infant weighed 5 pounds, 4 ounces at birth, and was breast fed for three weeks without much success. There was no appreciable weight gain, so supplementary feedings and then a number of formulas were tried. At 4 weeks the infant developed an eruption about the buttocks, considered by the mother at first to be a "diaper rash"; this gradually spread peripherally and finally involved both hands and

feet during the next week. A physician who was first consulted when the baby was 5 weeks old pronounced the child normal but for the rash which was attributed to "diapers" and "heat." No diagnostic tests were made and a salve was prescribed. There seemed to be some improvement at first, but the eruption grew worse during the next two weeks. Noisy breathing and a mucopurulent nasal discharge developed during the seventh week. There had been no apparent paralysis, and the baby had not "seemed sick." A second physician was consulted at a near-by hospital during the eighth week, and he immediately referred the patient here for therapy, with a tentative diagnosis of pemphigus and anemia.

Further history revealed that the father had been treated with penicillin for primary syphilis in May, 1947. The mother stated that she had been treated at the same institution and at the same time, but this could not be verified from the records there. One sibling, now 14 months of age, has seemed entirely normal to the mother. We examined him just last week in our clinic; he appeared well, presented no signs of syphilis, and serologic tests were negative.

At admission the clinical features of congenital syphilis in this patient were unmistakable. The infant really looked like "a little old man with a cold in the head"; she appeared malnourished, anemic, and had a generalized dusky maculopapular, vesicular, and pustular eruption which was most characteristic over the palms and soles. Where secondary infection did not interfere, the rash had a highly characteristic coppery hue with very fine and glistening superficial desquamation. There were ulcerations and excoriations about the nose, lips, and anus. There was a small mucosal "patch" over the hard palate. Scattered fine râles were heard over the right lung base; the liver and spleen were both firm, enlarged to a distance of about 4 to 5 cm. below the costal margins, and there was moderate generalized lymphadenopathy. No pseudoparalysis was noted.

A positive dark-field examination was secured immediately after admission. The hemoglobin level was 4.5 Gm. per cent, erythrocyte count 1.2 million per cubic millimeter, packed cell volume 14 per cent, leucocyte count 4,300 per cubic millimeter, with 15 per cent granulocytes, 4 per cent monocytes, and 81 per cent mature lymphocytes. Urinalysis showed nothing unusual. Both routine serologic tests were positive and the quantitative titer was 1,024 Kahn units; serologic tests from the 14-month-old sibling were negative. The infant's spinal fluid pressure was 120 mm. and the fluid was blood tinged, containing 4,000 erythrocytes, 26 lymphocytes, and 8 granulocytes per cubic millimeter; the protein level in the supernatant fluid was 31 mg. per cent and the sugar was 80 mg. per cent. Smears and cultures showed no organisms and complement fixation and colloidal gold curves yielded no abnormal results.

Therapy was started immediately—within three hours after admission—employing 100,000 units of penicillin G per kilogram of body weight divided into 100 equal doses given at three-hour intervals "around the clock." In addition, the infant has received several small transfusions, to date totalling 240 c.c., so that at present the hemoglogin level is 8.1 Gm. and the erythrocyte count is 3.8

million per cubic millimeter. Roentgenograms secured before starting therapy showed typical extensive syphilitic panosteitis and a hazy area of increased density in the base of the right lung; there were no abnormal physical signs over this area. The infant's course during therapy has been uneventful except for the fact that she developed apparent pseudoparalysis of the right arm on the twelfth day after the first dose of penicillin was given; this is still present.

DR. JOSEPH ROSENZWEIG (Resident, Tulane Division).—We often use a simple technique to obtain material for dark-field examination which is especially suitable when one does not have equipment for dark-field examination immediately available. One needs only a small piece of capillary tubing, like that used for smallpox vaccination and an ordinary sterile gauze square. Crusts or exudate are gently wiped off, then the clean surface of the lesion is irritated enough to produce a small amount of clear, serous fluid. The skin about the base of the lesion is compressed firmly between the gloved fingers for about five minutes. Tissue juice which then appears is drawn into a capillary tube, after which the ends are sealed with a flame. Such specimens can then be brought to the laboratory or held for several hours until examination can be conveniently done. The only precaution is to secure clear tissue juice; bloody specimens are difficult to examine.

At present we have three cases of congenital syphilis similar to this one on our service; among them we can demonstrate practically all the classical features of infantile syphilis. We just checked our records and found that we have treated 365 cases with penicillin since 1944; many more undoubtedly have been treated by other divisions here. Dr. Madey is visiting us from New York and I would like to know how this incidence compares with what he sees there.

DR. STEVEN MADEY (Exchange Resident, Tulane Division).—We see relatively few such cases at the Babies' Hospital because most of them are sent to Bellevue Hospital. The 1948 Public Health Reports indicated that there were 648 cases of congenital syphilis in New York City, and 13,309 cases for the entire United States. Congenital syphilis is still encountered too frequently elsewhere as well as here!

DR. RALPH V. PLATOU.—Judging by the last available national figures, syphilis accounts for four or five out of every 1,000 deaths under age one. We believe that many, if not most deaths attributed to infantile syphilis are due in reality to associated infections so common in these syphilitic babies. We believed this patient had a bacteremia and bacterial bronchopneumonia in addition to the syphilitic lesions Dr. Prather described; hemolytic *Staphylococcus aureus* has been cultured from some of the deep skin lesions, and a number of pathogens have been recovered from the upper respiratory tract, though blood cultures remained sterile. With the treatment schedule this baby is receiving—a total of 100,000 units of crystalline penicillin G per kilogram of body weight—the prognosis is excellent if our results with many other such patients can be taken as a guide. There is probably about a 5 per cent chance of relapse during the next four to eleven months.

DR. MYRON WEGMAN.—Why was treatment started so promptly after admission?

DR. PLATOU.—The clinical diagnosis seemed obvious and an immediate dark-field examination was positive. Results of routine laboratory tests, a battery of serologic tests, and results of spinal fluid examination were returned later, though specimens were, of course, secured before therapy was started. Particularly when there is secondary infection, I think that one is justified in starting treatment with penicillin even "on suspicion" of syphilis, provided that this is preceded by collection of appropriate specimens to establish or exclude the diagnosis retrospectively. Then, even if the child turns out to be nonsyphilitic he has not necessarily been "stigmatized" by such a "panacea" as penicillin, and no harm has been done.

DR. ELLEN MACKENZIE (Fellow, Tulane Pediatrics).—Why did pseudoparalysis appear after treatment?

DR. PLATOU.—I think that is probably a matter of timing. The expected natural course of healing in osseous lesions of syphilis, judged by roentgenograms, is not altered much by treatment and is probably accelerated significantly only when therapy with penicillin is begun very early.

Case 2. Ascariasis

DR. CRAVEN.—This is a 5-year-old Negro boy, whose illness began two weeks before admission. He had had irregular fever, night sweats, a dry hacking cough, and apparently real but poorly localized pains in his chest and abdomen. His appetite had failed and he had lost approximately 4 lb. during those two weeks. The family physician had found large left epitrochlear and axillary lymph nodes, together with a mild degree of generalized lymphadenopathy, and had suspected tuberculosis.

In addition to this lymphadenopathy, physical examination revealed coarse râles bilaterally and a large, smooth liver which extended 4 cm. below the costal margin; the spleen was not enlarged. The child was quite undersized and appeared chronically ill. Roentgenograms showed a diffuse infiltration through both lung fields which was considered to be compatible with a diagnosis of tuberculosis. Repeated Mantoux tests were negative, however, as were the blood cultures and "febrile" agglutination tests, including tularemia. The blood counts were not remarkable. Ova of *Ascaris lumbricoides*, cysts of *Endamoeba histolytica*, and *Giardia lamblia* were found in the feces.

The first three nights on the ward the patient's temperature rose to 103° F. (rectally). During this period he frequently cried out because of abdominal pain, and his bowels failed to move. An enema was given on the third day and twenty adult ascaris worms were expelled. The temperature then fell to normal and he was given hexylresorcinol, 0.6 Gm., this dose being repeated five days later. He passed about 80 large worms during this seven-day period.

Following his treatment there was remarkable clinical improvement as evidenced by a weight gain of 3 lb., absence of fever, and decrease in liver size. The x-ray gradually cleared.

Although the picture is confused by the presence of *E. histolytica* in the stool, we are inclined to attribute the fever, loss of weight, and hepatomegaly to ascariasis since these symptoms disappeared following treatment with hexylresorcinol and no amebacidal drugs were given. It appears likely, therefore, that the amebiasis is incidental; of course this still will be treated. Our problem here is in deciding whether or not the ascariasis was primary or simply activated or made evident by an acute febrile illness. We frequently see patients with pneumonia or tonsillitis in whom large numbers of worms are passed during the acute febrile illness. The worms are known to migrate in the presence of fever.

Our second problem is in deciding whether to treat the patient for ascariasis while the fever is still high or to wait until the fever subsides. At one time it was considered highly dangerous to treat such patients in the face of a high fever since it was thought that treatment might stimulate the worms to migrate outside the gut or to cause intussusception. Many now feel, however, that ascariasis should be treated immediately even though the fever is high, since the high fever is known to cause migration of the ascaris on its own, and hexylresorcinol is the best agent we have for inhibiting this migration. Dr. Beaver, would you like to comment upon the optimum time for treatment?

Dr. Paul Beaver (Tulane, Division of Parasitology).—In the past few years we have seen a gradual change in attitude regarding the optimal time for treatment. I think this change of attitude was prompted very largely by a tragic case of primary ascariasis. On admission the child was eliminating ascaris through the mouth and rectum. A large number of worms also migrated to the liver, in all probability several hours after admission, and the case ended fatally. The question arises whether or not that child might have been saved by prompt treatment. When the old drugs, santonin and oil of chenopodium, both of which are toxic, were to be used, there was reason for hesitancy. However, now with the use of hexylresorcinol, which is relatively nontoxic, early treatment should be instituted.

Dr. Craven.—Dr. Beaver, an interesting feature of this case was the marked hepatomegaly which we found difficult to explain.

Dr. Beaver.—With the migration of ascaris larvae from bowel to lung there are always a certain number of worms which get sidetracked, some of which may be screened out by the liver.

Dr. Platou.—How can you say this is primary ascariasis with ascaris pneumonitis instead of ordinary bronchopneumonia in a child who has adult ascarids in the intestine?

Dr. Craven.—That was a difficult question to answer when the patient was admitted. However, the diagnosis was made chiefly as a result of the patient's clinical course in the hospital. The patient did not present typical physical findings of acute bronchopneumonia. The blood count did not indicate any acute ordinary bacterial infection. The x-ray appearance resembled miliary

tuberculosis more than acute bronchopneumonia. He did not receive sulfonamides or antibiotics, and his response was attributed to hexylresorcinol.

DR. PLATOU.—Has anyone ever isolated the larvae of ascaris from human lungs during life?

DR. BEAVER.—The larvae have been found in sputum, but they are very difficult to find. There are two ways in which larvae get lost in this migration from bowel back to bowel. One of them, perhaps the most common one, is by being lost in the liver. But there are also a great many lost by expectoration. If you can collect exudates in large quantities you have a fair chance in these very heavy infestations of finding at least one larva but you would need a large volume of sputum with which to work.

DR. ROSWELL JOHNSON (Tulane, Department of Pediatrics).—Dr. Beaver, do you think that eosinophilia is necessary to establish a diagnosis of pulmonary ascariasis?

DR. BEAVER.—Let us put it this way. We are always much more convinced of the diagnosis if eosinophilia occurs. This patient had just a low-grade eosinophilia, 4 per cent.

DR. RICHARD FOWLER (Resident, Louisiana State University Division).—Would you defer treatment with hexylresorcinol in the presence of diarrhea?

DR. BEAVER.—No, I would not.

DR. A. L. EXLINE (Resident, Tulane Division).—Do you use repeated courses of hexylresorcinol if the eggs persist in the stool?

DR. BEAVER.—We have seen courses of hexylresorcinol repeated every other day for as many as four times without observing any ill effects.

DR. SIDNEY CHIPMAN (Louisiana State University Department of Pediatrics).—Do you mean to imply that all larvae perish in the liver and that finding an adult ascaris in the liver indicates migration up through the bile duct?

DR. BEAVER.—Yes, the larvae either perish in the liver or pass on through to the lungs.

DR. JOHNSON.—Is there any available effective treatment for ascaris pneumonitis per se?

DR. BEAVER.—No.

DR. WEGMAN.—In view of all the publicity that has been given to amebiasis these past few years, it is interesting to see a case of ascariasis and amebiasis in which the ascariasis is emphasized and the amebiasis played down.

DR. BEAVER.—Presumably this child has had amebiasis for some time. He is one of the many in this part of the world who likewise have amebiasis, and frequently have other unrelated infections.

Case 3. Sickle Cell Disease

Dr. William Stewart (Resident, Louisiana State University Division).—This 6-year-old Negro girl was admitted with the chief complaint of pain in her legs of one week's duration. One week prior to admission the child began to complain of severe pains in her calves and thighs. The pains were so severe she would not allow anyone to touch her legs and she refused to walk. About this same time she began to have some fever, developed anorexia, and vomited occasionally. The family noted that her eyes turned slightly yellow and that her skin appeared to be paler. She was kept in bed and given Aspirin tablets with very little relief. After the symptoms had continued one week without abatement she was brought to the hospital and admitted.

The past history obtained from the patient's cousin revealed that she was in Charity Hospital at the age of 11 months for osteomyelitis of the right foot from which she recovered completely. The past history also shows that since the age of one year she has complained of periodic pains in her legs which are occasionally accompained by fever.

The family history and social history were noncontributory. There was no history of anemia in other members of the family.

The physical examination on admission showed a thin, pale little girl, quite dyspneic and very uncomfortable. The temperature was 102° F., the pulse rate 140 per minute, and the respiratory rate 35 per minute. The sclerae were not jaundiced and the conjunctivae were very pale. The lungs were clear. The heart rate was rapid with a gallop rhythm and the heart was enlarged to the left and downward, with the PMI in the sixth interspace one centimeter outside the midclavicular line. There was a loud, blowing, systolic murmur heard best in the second left interspace but audible over the entire precordium and over the left scapula. The abdomen was soft, with the liver palpable 6 cm. below the costal margin. The spleen was not felt. There was marked tenderness and pain on motion in both lower extremities. There was no joint tenderness.

The blood count on admission showed 2.5 Gm. of hemoglobin, 1,200,000 red blood cells, 33,000 white blood cells (corrected for normoblasts), 120 normoblasts per 100 white blood cells, 10.5 per cent reticulocytes, 98 per cent sickling in twenty-four hours. The urine was negative. The one-minute direct serum bilirubin concentration was 0.6 mg. per cent and the total serum bilirubin 1.4 mg. per cent.

Shortly after admission the old chart from her previous admission at the age of 11 months was made available and revealed that at that time she had 7 Gm. hemoglobin, 2,800,000 red blood cells, 70 to 80 normoblasts per 100 white blood cells, 9.5 per cent reticulocytes, and 100 per cent sickling.

The day following admission she was given a transfusion of 250 c.c. of whole blood. After this transfusion the pulse rate slowed, she was less dyspneic, and the pains in her legs lessened but did not disappear entirely. The next day, however, her temperature again rose and she developed severe pains in the legs and abdomen. The abdomen became boardlike and very tender, and she looked much more severely ill. One hundred per cent oxygen was administered with

an OEM mask.* At first she struggled against the mask but after she began to get relief she accepted it and asked us to leave it in place. Within twenty minutes the abdomen became soft and within thirty minutes she fell asleep. The next day her temperature was normal and she had no further pain. She was given two more transfusions of 250 c.c. of whole blood on subsequent days. The hemoglobin is now 10.5 Gm., the pulse rate has become normal, there is no more dyspnea, the systolic murmur has disappeared, and the liver has decreased in size. She now complains only of an occasional ache in her right leg.

DR. WEGMAN.—Sickle cell anemia is hardly a rare thing in our experience and we have had many patients with it brought here to our conferences. There were two or three points in this case, however, which we thought might be of interest for discussion. One thing was the marked degree of anemia that this child had. Another was the tremendous percentage of normoblasts. We should like to get Dr. Johnson to discuss this point in a few minutes. The large number of normoblasts made me suspect Mediterranean anemia, but after repeated preparations for sickling, the resident staff convinced me we were dealing with sickle cell anemia. In consulting the textbooks on the question of normoblasts in sickle cell anemia one is told that normoblasts are not common in this condition. A paper by Tomlinson, however, dealing with abdominal crises in sickle cell anemia, refers to one case in an 11-year-old girl in which there were 116 normoblasts per 100 white blood cells and also a very high reticulocyte count.

Another point that interested me was the dramatic response to 100 per cent oxygen. After she had once become accustomed to the use of the mask, the change in her condition with the administration of 100 per cent oxygen was striking. It was not only a matter of subjective disappearance of pain but a striking change in the condition of the abdomen as well. We were all very much impressed. Perhaps Dr. Ordway will explain the mechanism to us after we get Dr. Johnson to discuss the high normoblast count.

DR. JOHNSON.—This child's normoblast count was certainly higher than one usually sees. Such responses in children are very much akin to those one sees in adults, where the degree is proportionate to the severity of anemia. This child was about as anemic from a severe depletion of her circulating erythrocytes as one ever sees. The usual normoblast count in sickle cell anemia is 20 to 30 per 100 white blood cells. I think it is interesting here to point out the absolute value of the two constituents in question. We frequently are misled when we speak of nucleated red cells in proportion to white cells. This is a thoroughly confusing concept with no basis or justification whatsoever except for correcting a white blood count to its true value. This child had 33,000 white cells corrected and since she had more nucleated red cells than white cells her nucleated red cell count per cubic millimeter was, for purposes of rough discussion, about 40,000 per cubic millimeter. This is, of course, an extremely high count. Now her reticulocyte count was 10.6 per cent of her red blood count, which was extremely low, giving her roughly 120,000 reticulocytes per

*This is a mask equipped with a reservoir bag having inspiratory and expiratory valves; it permits the inhalation of 100 per cent oxygen with negligible rebreathing and accumulation of CO_2.

cubic millimeter. The average healthy child who has a red count of approximately 4,500,000 and a reticulocyte count of 1.5 per cent, is going to have about 67,000 reticulocytes per cubic millimeter. The patient, then, has an unbelievably low reticulocyte count. This brings up a point which I have repeatedly made here each time a discussion of reticulocyte counts comes up: it usually takes several counts, done by different techniques, to make sure what the reticulocyte count really is. It would be extremely uncommon to have such a high number of nucleated red cells and so small a number of reticulocytes, because with a bone marrow doing everything possible to effect a physiologic compensation as demonstrated by the normoblast count, I am inclined to believe that her reticulocyte count was actually closer to 70 or 80 per cent. One other point of interest is the problem of differentiating or trying to differentiate between sickle cell trait and sickle cell disease. Tests for such differentiation have only questionable validity. It is well known that some people with the so-called sickle cell trait will show the disease, with the same picture at autopsy as those who have had sickle cell disease. Of course one can say that the diagnosis in such cases was in error during life and that the patient actually had sickle cell disease. I am not sure if that strict differentiation between sickle cell trait and sickle cell disease necessarily holds. There are various techniques to distinguish between the two and to demonstrate sickling, but none of these are physiologic.

Dr. Nelson Ordway (Louisiana State University Department of Pediatrics).—When we give 100 per cent oxygen we raise the oxygen tension of arterial blood by several hundred millimeters of mercury, and its content by about two volumes per cent. Assuming that the A-V oxygen difference remains the same, we would expect a rather appreciable rise in the venous oxygen saturation, of the order of about 20 per cent, if the patient's hemoglobin concentration is 8 Gm. The concommitant rise in the oxygen tension of the venous blood would be about 10 to 15 mm. of mercury. Now if the presence in the capillaries of thrombi composed of sickle cells is the basis for the crisis that these patients have, and since the tendency of the cells to sickle is inversely proportional to oxygen tension, it may be that the administration of oxygen, by increasing the tension all through the circuit, causes these thrombi to break up, thereby improving the circulation of blood through the capillaries and alleviating tissue anoxia. A further effect of the inhalation of oxygen in high concentration is the immediate production of a mild respiratory acidosis with increase in carbon-dioxide tension and decrease in pH. It is conceivable that the clinical improvement may be related to the altered acid-base balance.

Dr. Wegman.—The authors of the article I referred to previously made a great point of the importance of anoxia and postulated a vicious cycle of anoxia and obstruction to circulation. The promptness with which this particular child responded to administration of oxygen was striking and made us wonder if it could be related to the "breaking up" of thrombi.

When I told Dr. Platou that we were going to present this case today he asked if we were going to use it as a point for discussion of the confusion that may exist between rheumatic fever and sickle cell anemia. As you remember,

the presenting complaint in this child was joint pain and she has had some joint pain since admission. In both this child and a similar one in whom we tried 100 per cent oxygen when joint pain was present, no improvement was shown, but Dr. Stewart is pretty well convinced that the oxygen did not have a fair trial.

DR. PLATOU.—The diagnosis of sickle cell disease was not made when this child was 11 months old?

DR. STEWART.—Yes, the diagnosis was definitely made.

DR. PLATOU.—We have a local empiricism to the effect that dactylitis under 6 months usually is due to syphilis, after 6 months it is usually tuberculous, but at any age in a Negro it should be considered to be due to sickle cell disease until proved otherwise. I do not know how many of these we have seen but it would be interesting to add them up sometime; their number should be considerable. Reviewing the old chart some time ago, it seemed to me that the diagnosis of sickle cell disease was discarded at the age of 11 months in favor of osteomyelitis.

DR. STEWART.—No, the correct diagnosis was made then; the error came in "signing out" the chart; the correct diagnosis was not entered properly on the face sheet.

DR. WILLIAM OBRINSKY (Louisiana State University, Department of Pediatrics).—How do you account for five years of freedom from symptoms?

DR. WEGMAN.—I doubt if they were free. It is lucky that this child got away with her disease over this period of time, but it is very unfortunate that she did not have health supervision. I believe that is a serious lack in our follow-up program outside of the hospital. If she had 7 Gm. of hemoglobin then, I should imagine she has been getting along with a very low hemoglobin ever since.

DR. OBRINSKY.—But no frank crises?

DR. WEGMAN.—No.

DR. DANIEL STOWENS (Tulane, Department of Pediatrics).—Working on the basis of Dr. Tomlinson's ideas about the mechanisms for sickle cell crisis, we began treating patients in crisis with plasma rather than with whole blood. This was done somewhat empirically with the idea of "ballooning out" the whole vascular system. For a period of a year in which I saw these patients in great numbers, we were very much impressed by responses we got with plasma. We tided them over the crisis usually within twenty-four to forty-eight hours and *then* gave them whole blood transfusions. We never bothered to transfuse them to levels above 8 or 9 Gm. of hemoglobin, as they would not maintain higher levels very long.

DR. WEGMAN.—Dr. Kelly, when he came on rounds the next day, questioned whether we were not rather rash in transfusing this patient right away.

DR. ROY KELLY (Resident, Louisiana State University Division).—Yes, I want to know the arguments for and against transfusing patients with sickle cell

anemia in crisis. It has been said, particularly here in the Obstetrics Department, that a great deal of difficulty is seen in patients who have obstetrical complications during a crisis for which blood seems to be required. I would like to know more about this mechanism.

DR. STOWENS.—That is another point in the administration of plasma. With the peculiarities of the sickle cell, by giving plasma and oxygen we were able to increase the oxygen tension of the plasma and thereby decrease tissue anoxia.

DR. JOHNSON.—Transfusions should be avoided during these crises if possible. Oxygen is the best single therapeutic agent. Salt-poor albumin can be used to maintain blood volume. Another point to be considered here is why save such a patient from sickle cell anemia only to have her die later from serum hepatitis?

DR. STOWENS.—I think we see many more examples of sickle cell crisis than of serum hepatitis; the risk of hepatitis seems quite unimportant in this particular case.

DR. JOHNSON.—I am not so sure that this girl has been neglected. Had she been transfused many more times during the past five years she would probably have nothing more than she has now except more hemosiderosis. She is now using her iron supplies to build new blood.

Psychologic Aspects of Pediatrics

THE GIFTED CHILD

"To Them That Have"

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THE term *gifted* is applied to individuals who are endowed with superior natural mental abilities which clearly differentiate them from the average of the same age and experience. In the larger researches, the term has been limited to children with intelligent quotients (I.Q.) of 140 and over, who normally constitute about 0.5 per cent of the population.

In 1921, Dr. Louis Terman of California and a group of associates began a long-term study of gifted children to determine what sort of adults they grow up to be. With this aim in mind over 1,500 children out of a total school population of about a quarter million were selected from the grade and high schools of California on the basis of excellence in school performance and high rating on intelligence tests. These individuals have now been observed for over twenty-five years and they form the basis of a recent publication by the California group of psychologists.[1]

DESCRIPTION OF THE GROUP

Intelligence.—The original plan was to include only children with an I.Q. of 140 or above, but for various reasons sixty-two subjects with I.Q.'s between 135 and 140 were included. Most of the latter were either siblings of subjects who had already been accepted in the experimental group, or they were older adolescents whose scores seemed spuriously low because the test used at the beginning of the study (the 1916 Stanford-Binet test) does not measure high intelligence in older children with sufficient accuracy.

Since it was impossible, for financial reasons, to test all the school children, teachers were asked to name the brightest children in their classes as well as the youngest. The selected children were then given mental tests. It is of interest that the youngest child in the class qualified more often for inclusion in the gifted group than did the brightest children. Relative youth proved a better gauge for predicting intelligence than the teacher's judgment.

The mean I.Q. for the entire group was approximately 150. One girl scored 200. Six children had I.Q.'s between 190 and 194.

Sex.—There were somewhat more boys than girls (116.4 boys to 100 girls). That the preponderance of boys was not due to biased selection on the part of the teachers is indicated by the fact that of those nominated who failed to qualify for the gifted group, the proportion of males to females was the same

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as that in the general population—103.7 boys to 100 girls. Terman presents evidence in favor of the view that the larger number of boys in the gifted group is due to greater variability among them,[2] but he is unwilling to make any positive statement.

National Origin and Race.—In comparison with the general population of the cities concerned there was a 100 per cent excess of Jewish children, a 25 per cent excess of children of native-born parentage, a probable excess of children of Scottish parentage, and a deficiency of Italian, Portugese, Mexican, and Negro ancestry. However, nearly all the national and racial groups contributed one or more subjects to the study. "No race or nationality has any monoply on brains." In part, at least, the representation by some groups was limited by handicaps of language, environment, and educational opportunities.

The parents of the gifted children were principally from the professional group (31.4 per cent) and the semiprofessional and business group (50 per cent). The median income for a sample of the families was more than twice that of California families in general.

Medical History and Physical Status.—No striking differences were found in the medical history and physical status. The proportion of breast-feeding was considerably in excess of that in the general population. The gifted children started to walk and talk a little earlier than others. Pubescence was also accelerated on the average. They were, if anything, less "nervous" than the generality of children. Though twice as many wore glasses as others, the incidence of defects of vision was no more frequent. In the gifted group, presumably, defective vision was more often corrected by glasses. The incidence of tonsillectomy was about twice as great as among others.

The frequency of physical defects and abnormal defects of any kind was below that found in most medical surveys of school populations. On the whole the typical gifted child was found to be a slightly better physical specimen than the generality of children as indicated by body measurements, healthy histories, and medical examinations.

Educational History.—The children liked school and most of them had skipped grades. None had been left behind. Nearly one-half had learned to read before going to school. Early indications of superior intelligence most often noted by the parents were quick understanding, insatiable curiosity, extensive information, retentive memory, large vocabulary, and unusual interest in such things as number relations, atlases, and encyclopedias.

Objective tests showed that the gifted children were 44 per cent above the average child in school achievement, indicating that the superior group, though generally advanced in school, could actually have done higher grade work. Terman estimates that more than one-half of the children with I.Q's of 135 and above had already mastered the curriculum to a point two full grades beyond the one in which they were enrolled and some of them as much as three or four grades beyond. The superiority of the gifted child did not relate equally to all the subjects. It was greatest in reading, language usage, arithmetical reasoning, and information in science, literature, and the arts. It was less marked

in arithmetical computation, spelling, and factual information about history and civics. But even in these subjects the gifted child surpassed the average. No correlation was found between the child's ability to achieve at school and the amount of formal schooling he had received. One child had had only two years of schooling before he entered Stanford University at 14 years of age.

The principal interests of the group under study were reading and collecting. Their play activities did not differ materially from those of the general group, although the gifted girls tended to be a little more masculine in their play life than other children. In general the play interests corresponded to those of children two to three years older.

The gifted children were found to be superior in character tests. They were less likely to be boastful or to overstate their knowledge and they were more trustworthy when under temptation to cheat. They were, as a group, more stable emotionally.

THE GIFTED GROUP AS ADULTS

As adults the gifted group showed some loss of I.Q. Terman is of the opinion that the decrease can be accounted for, in good part if not entirely, by errors in measurement and by the failure of tests in adults to measure the same mental functions as are measured by the much better standardized tests for children.

Mortality.—By 1940, when the mean age of the gifted individuals was 30 years, the death rate among male subjects was 4.14 per cent and among females 3.98 per cent, as compared with 5.02 per cent and 4.68 per cent, respectively, for comparable age groups in the general population.

Height.—The height of gifted men, as reported by themselves, averaged 5 feet, 10.65 inches, more than 2 inches above the average for unselected college men. The gifted women were .69 inches taller than the average college woman. There is, however, reason to believe that men tend to overstate their heights. Terman concludes that gifted men probably average about one-half inch taller than college men in general and gifted women show the same difference.

Physical health seemed to be at least as good as in the general population.

Mental Health.—The incidence of insanity in gifted subjects was slightly below that of the population as a whole. Alcoholism was uncommon and juvenile delinquency low. Slightly more than one per cent of the group had a history of homosexuality. About one-half of these had made reasonably normal heterosexual adjustments.

Educational Histories.—About 90 per cent of the gifted men and 80 per cent of the gifted women entered college, and 70 per cent of the men and 68 per cent of the women graduated. This percentage is approximately eight times as great as for the general population in California. In undergraduate years the social sciences were first choice as a major field by both men and women.

Of those who graduated, 68 per cent of the men and 60 per cent of the women returned for graduate study. About one-half of the men and one-third of the women received graduate degrees. A law degree was taken most fre-

quently, with the M.A., Ph.D., and M.D. following in that order. Fifty-two received the M.D. degree.

Though the average grade in college was superior, it was not always as high as might have been expected. Almost 8 per cent of the men and 2 per cent of the women flunked out. The average I.Q. of those who failed was slightly below that of the graduates. Failure was attributed to habits of idleness, unwillingness to do routine assigned tasks, excessive amount of work for self-support, or the deliberate choice to give preference to social and extracurricular activities. Occasionally physical illness and social maladjustment or immaturity were factors.

More than one-third of the men who graduated earned one-half or more of their undergraduate expenses, as compared with 16 per cent of the women. Less than 23 per cent of the men graduates earned none of their expenses.

The gifted individuals participated in extracurricular activities to a greater extent than the average students.

Occupation.—Almost one-half of the gifted men chose one of the professions as a career and about one-fourth more were in semiprofessional or higher business occupations. On the whole, they were filling positions of responsibility and leadership to a greater extent than the average college graduate. A few (6 per cent), however, were employed as minor clerical workers, policemen and firemen, and semiskilled craftsmen. One worked as a truck driver and six were in occupations requiring little skill, training, or ability. Twelve per cent were engaged in farming and other agricultural pursuits. Only 6 per cent of the group entered medicine but it is gratifying that the highest median income among the professions was earned by physicians.

Income.—On the whole the earned incomes of the members of the gifted group were higher than those of college graduates in general and considerably higher than those of unselected men and women. The men in the semiprofessional and business group had the highest incomes, the professions came next, and the clerical workers, salesmen, retail business, and skilled trade occupations ranked third. The college graduates did better, financially, than the nongraduates.

Avocational Pursuits.—A characteristic of the gifted person is an active interest in avocational pursuits. Nearly two-thirds of the group reported active interest in two or more of these and one-third reported three or more. Sports held first place among both men and women with photography second among men and music second with women. Music rated third with men, gardening with women. As for amount of interest in twelve specific fields, travel and science were first among men and travel and literature among women. Religion rated lowest with both sexes. On the whole, men who were successful in their vocations had greater interest in outside fields than the men who were least successful. In reading, literature and history were by far the most popular among both men and women. More women than men preferred fiction.

Politics.—As to political alignment, 45.2 per cent of the men and 41.6 per cent of the women said they were "Republicans" or "conservatives" and 40.0

per cent of men and 41.3 per cent of the women classified themselves as "liberal," "New Deal" or "Democrats." The number of radicals was very small. Among the professional groups author-journalists rated themselves as by far the most radical. Chemists, physicians, engineers, and lawyers were the most conservative, with teachers holding an intermediate position. The higher income groups were more conservative than the lower. There was no difference between the college graduates and nongraduates. In both sexes the tendency toward socialism was greatest among those whose emotional life was rated as unsatisfactory.

Subjects with very much interest in science or politics were more radical than others. Jewish men were slightly more radical than the non-Jewish; the Jewish women were distinctly more radical. There were fewer extreme scores, either radical or conservative, among the Jewish than the non-Jewish subjects.

Marital Status, Offspring.—Both men and women in the gifted group married as frequently and at about the same age as the California population as a whole. However, the incidence of marriage was greater and the age at the time of marriage lower than among college graduates in general. The difference was especially striking for the women. As might be expected, the gifted individuals chose spouses of comparably high intelligence. Nearly three-fourths of the husbands and over two-thirds of the wives had attended college for one or more years.

The average number of children of the gifted individuals who had been married five years or more was 1.52. The mean I.Q. of 384 offspring was 127.70. There was a low incidence of feeble-mindedness and border-zone mentality. The proportion of children with an I.Q. of 150 or over was about twenty-eight times that expected in the general population. The mortality among offspring was far below that for the general population.

The divorce rate by 1945, when the average age of the group was a little below 35 years, was 14.4 per cent for the men and 16.3 per cent for the women. It is not possible to make comparisons with the population in general or with college graduates since accurate data for these latter groups are not available. In the gifted group divorcees were less than one-half as frequent among college graduates as among nongraduates.

Subjects of I.Q. 170 or Over.—Among the living gifted group in 1940 there were forty-seven men and thirty-four women with I.Q. of 170 or more. In the general population only about three children in 10,000 may be expected to test as high as this. The high group learned to read earlier than the remainder of the gifted group and they completed grade school 8.4 months younger. They were graduated from high school and college about 9.6 months younger but the difference was not marked for the women. The high group did not differ materially from the others in physical health, nor was any difference found in "nervous symptoms" or "mental adjustment." This is of particular interest since the individuals with very high I.Q. have been considered especially prone to neurotic behavior. Social adjustment was as good as for the gifted group as a whole.

The high group did exceptionally well at college. However a good many of them did not achieve as well as might be expected. They chose, for the most part, the professions (61.6 per cent as against 45.4 per cent for the group as a whole). Of the twenty-seven men in the professions none chose medicine; nor, for that matter, did any of the very high I.Q. women. The average income did not differ materially from that of the gifted group as a whole.

THE PROBLEM OF SCHOOL ACCELERATION

Terman discusses at some length the problem as to whether children of high I.Q. should be allowed to become accelerated in school or whether they should remain in classes with children of their own chronologic age. A third alternative is to provide special classes with an enriched program for the gifted. There are such classes in many communities and it is Terman's opinion that their value has been thoroughly demonstrated. Unfortunately they are available to only a small minority of gifted children and the choice therefore rests between acceleration and nonacceleration. Terman concludes that, by and large, children of 135 I.Q. or higher should be promoted sufficiently to permit college entrance by the age of 17, or, better, 16 years. The risk of maladjustment when a young child of high I.Q. is put with older children of his same mental age is less than is commonly believed. There is, on the other hand, a very real danger that the bright child, in a class with children of his own chronologic age, will fail to develop the ambition and habits of work necessary for success in college.

FACTORS IN THE ACHIEVEMENT OF GIFTED MEN

An important part of the Terman study has been to discover what factors and circumstances are correlated with adult achievement. Although most of the individuals in his gifted group achieved positions of eminence and leadership, a sizable proportion chose lowly positions in which their intelligence level could be of little use to them or they failed to attain more than average success in their chosen professions.

In order to assess the factors which make for vocational success or failure the most successful members of the group were compared with the least successful. The selections were made by three judges working independently. Each case on which there had been disagreement was discussed and a final decision was made by majority vote. The primary criterion of success was the extent to which a subject had made use of his superior intellectual ability. If he had chosen a university career or a profession, recognition in the chosen field counted heavily and earned income received little weight unless it seemed to be a measure of success. In business or the semiprofessional pursuits, on the other hand, earnings were given more consideration. The study was limited to men since the criteria for success in women are so difficult to estimate.

To make the contrasts as sharp as possible the 150 most successful men (Group A) and the 150 least successful (Group C) were selected for study.

The A group included all men who were listed in *Who's Who* and in *American Men of Science,* a large majority of those whose university rank was above

that of instructor, and men who were outstandingly successful in the professions and in business, as well as a few who achieved most in literature, art, motion pictures, or radio.

Though the C group consisted principally of men in skilled and semiskilled trades, clerical and minor business positions and civil service jobs, it also includes a few classified as professional, semiprofessional, and managerial whose records of accomplishment were unimpressive. The average I.Q. of the A's was slightly greater than that of the C's but there was much overlapping of scores. In fact the mean of the C's was so high as to be equalled by only 15 per cent of students in superior universities.

Earned Income.—Though earned income was given relatively little weight in classifying the subjects, the average income for the A's was more that 2.5 times that of the C's.

Amount of Education.—Ninety per cent of the A's had graduated from college and 76 per cent had done one or more years of graduate work. The corresponding figures for the C's were 37.2 per cent and 14.7 per cent. Difference between the two groups in school achievement were already apparent in high school and became more marked at the college level.

Vocational Interest.—More of the members of the A group than the C group had chosen their lifework and liked their work. On the other hand, more of the C's had drifted into their jobs and almost five times as many as A's said that they would prefer some other kind of work.

Family backgrounds differed markedly for the two groups. More than three times as many A fathers as C fathers had graduated from college and there was a similar difference for the siblings. More than twice as many of the A farthers as C fathers were in the professional class. There were three times as many individuals of Jewish descent among the A's as among the C's. Childhood ratings for emotional stability, social adjustability, and various traits of personality were lower in the C's than in the A's. There was no difference in physical health.

Marriage.—The marriage rate was lower for the C's than the A's but the incidence of divorce was twice as great. The A's chose wives who were more nearly their mental equals as indicated by mental tests and amount of schooling.

Personality Ratings.—The A's rated far higher than the C's in perseverence, self-confidence, integration toward goals, and absence of inferiority feelings. The A group also outranked the C's in appearance, attractiveness, alertness, poise, attentiveness, curiosity, and originality. All in all the greatest contrast between the two groups was in the drive to achieve and in all-around social adjustment. Terman points out that contrary to the view of many to the effect that great achievement in usually associated with emotional tensions which border on the abnormal, in the gifted group success was associated with a well-balanced temperament and the absence of excessive frustration.

APPRAISAL OF ACHIEVEMENT

Terman's study shows clearly that superior mentality in childhood is predictive of superior achievement in adult life. Twenty-five years after the subjects were selected solely on the basis of a high intelligence score, almost one-half of the men and more than one-half of the fully employed women are in one of the professions and another 30 per cent of the men are in the semi-professional and higher business category. During the depression, when 15 to 20 per cent of the employable males in California, where the study was carried out, were out of work, the proportion of unemployed among the gifted men was not over one per cent. Nearly 70 per cent are college graduates and 29 per cent took graduate degrees. Earned income was considerably above average.

By the end of 1945, when the average age of the subjects was close to 35 years, about ninety books or monographs and about 1,500 articles had been published by members of the group. Patents granted to members of the group number more than 100. The group includes twenty to twenty-five scientists whose achievement has already won for them a national reputation or appears likely to do so. Among the best candidates for outstanding achievements are a dozen or more of the men who have gone into medicine.

WAR RECORDS

Military Service.—Of the 760 men on whom information was secured, 42.5 per cent served in the armed forces during the war and an additional 1.2 per cent were in the Merchant Marine. Six men registered as conscientious objectors. In view of the fact that more than one-half of the gifted men were over 30 years of age when America entered the war, it is noteworthy that the proportion enrolled in the armed services exceeded that for all males in the country aged 18 to 44 years. Terman estimates that the number rejected as physically or mentally unfit was far below the average for the country as a whole.

Though about one-half of the men in the Army entered as privates, 70 per cent were commissioned officers at the time of discharge and 75 per cent of the men were commissioned officers on discharge from the Navy. With the records still incomplete, 22 per cent of the men received one or more citations.

Many more of the A's than the C's received commissions. In the A group, 82 per cent were discharged as commissioned officers in the Army and 89 per cent in the Navy. The corresponding percentages for the C group were 33 and 13.

SUMMARY

1. Terman's follow-up study of gifted children into adult life is reviewed. The study was begun in 1921 and the average age of the group in 1945 was 35 years.

2. Gifted children are, as a rule, superior to the general child population in physique and general health and the later mortality up to the age of 35 years is lower. It is not clear how much of this is to be credited to better home environment.

3. Throughout the educational period, the achievement of gifted children is superior to others, although a good many make poor or mediocre records in college.

4. The achievements of gifted children are versatile rather than one-sided, and they generally do well in all school subjects.

5. The typical gifted child is customarily held to a grade well below his ability.

6. Gifted children who have been promoted rapidly are, as a group, superior to gifted nonaccelerates in health and general adjustment. They do better school work and are more successful in their later careers.

7. Gifted children average above the general child population in character and personality tests and trait ratings. They are more stable emotionally and better adjusted socially.

8. Up to age 35 the gifted group shows a normal or below normal incidence of serious personality maladjustment, insanity, delinquency, alcoholism, and homosexuality.

9. Children of very high I.Q. (above 170) do better at school than lower testing individuals; they are not more prone to serious maladjustment; and they are more successful vocationally.

10. As adults, the gifted group is well above the average college graduate in vocational achievement. They marry more often than other college graduates and marital adjustment is better. The divorce rate is lower.

11. There is a tendency for the I.Q.'s of the offspring of gifted adults to regress toward the mean, but the mean I.Q. (127) of the children is much higher than that of average children (I.Q. 100).

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Comments on Current Literature

AUREOMYCIN AND PERTUSSIS

THE severity of pertussis varies considerably from year to year, and also from patient to patient. It is generally agreed, however, that the infection may be a serious disease, especially when it occurs in infants under the age of 6 months. According to Gordon and Almaden[1] the mortality rate in pertussis for the United States is 2.3 per cent, and for the state of Arkansas in 1947 it was 3.3 per cent. These authors have stressed the age factor, pointing out that in their analysis of fatalities due to pertussis 40 per cent of the deaths occurred in infants under 3 months of age and 68.5 per cent occurred in patients under 6 months of age.

In general, therapy of whooping cough has not been satisfactory. Prevention of the disease by active immunization is highly desirable and has gained popularity in recent years. Nevertheless, pertussis still occurs and improved therapeutic methods are needed. While the development of hyperimmune human antipertussis serum has been accepted as a therapeutic advance, and more recently the value of streptomycin has been demonstrated in a small series of patients,[1] a specific and effective therapeutic agent in the treatment of pertussis is still an urgent need.

Recently Joseph A. Bell, Margaret Pittman, and Byron J. Olson (May 13, 1949, issue of *Public Health Reports*)[2] demonstrated the therapeutic effectiveness of aureomycin in experimental animals and reported preliminary clinical trials. White Swiss mice were inoculated intracerebrally with suspensions of *Hemophilus pertussis*, and then treated with aureomycin. By varying the approximate number of organisms in the intracerebral inoculum, the dosage of antibiotic, the time intervals of antibiotic administration, and the duration of treatment, these investigators attempted to gain a general idea of the most satisfactory treatment regime. They concluded on the basis of these observations that aureomycin is an effective agent in the treatment of *H. pertussis* infection of white Swiss mice, and that a "treatment regime of small doses given at frequent intervals over a period of several days was more effective than larger doses given singly or at infrequent intervals for a few days." Encouraged by the results of the experimental studies in mice, this group undertook an evaluation of the therapeutic effectiveness of aureomycin in human pertussis. Since members of this team have been engaged in a study of pertussis in Norfolk, Va., for a period of ten years, it would seem that even a preliminary evaluation of the antibiotic in patients in that community might be of real statistical value.

The treatment schedule was designed for home use, and a total of 20 patients was treated. Aureomycin was administered by mouth in sweet cherry syrup, beginning on the second to the seventeenth day following onset of the paroxysmal cough. In the first eight cases a total dose of 0.5 Gm. aureomycin per kilogram of body weight was given in divided doses over a period of four days. The remainder of the patients received the same total dosage distributed over an eight-day period. When vomiting occurred following administration, the dose was repeated. Patients ranged in age from one month to 6 years. Since paroxysmal coughing often attended by whooping and vomiting is considered a characteristic clinical manifestation of pertussis, the duration, frequency, and

intensity of the paroxysmal cough were the chief criteria for evaluating the effect of the therapeutic agent. Comparing the duration of paroxysmal cough in the twenty treated cases with 380 untreated controls (Bell and associates, Table 5), the authors concluded that "... aureomycin given orally in apparently nontoxic doses shortened the clinical course of the disease." "In only a few," however, "particularly the cases treated early, was the response ... dramatic in the sense that complete recovery immediately followed a few days' treatment."

TABLE 5. DURATION OF PAROXYSMAL COUGH IN TREATED AND UNTREATED CASES OF PERTUSSIS[2]

	INTERVAL ONSET PC TO TREATMENT (DAYS)	YEAR OF OCCURRENCE	TOTAL CASES	DAYS DURATION OF PAROXYSMAL COUGH			
				< 20	20-29	30-39	40-PLUS
Untreated cases		1938-42	165	11	25	42	87
		1942-47	215	14	29	47	125
Total			380	25	54	89	212
Aureomycin treated cases	2-10	1949	7	7	0	0	0
	11-17	1949	13	0	10	2	1
Total			20	7	10	2	1
Expected number of treated cases if distributed like untreated cases			20	1	3	5	11

While the results of this preliminary report cannot be accepted as proof that aureomycin is a specific for *H. pertussis*, one gains the impression that this antibiotic seems to have a beneficial effect on the clinical course of the disease. In these preliminary trials the lack of adequate controls, which would have involved the treatment of alternate cases of similar severity in the same epidemic, is a reasonable objection. It must be recognized that the role of secondary bacterial invaders is of paramount importance in the clinical evaluation of any therapeutic agent in the treatment of pertussis.

If aureomycin or other antibiotics administered by mouth should prove effective in the treatment of pertussis, home care of a large number of patients will certainly improve the mortality statistics in this important pediatric disease.

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REFERENCES

1. Gordon, Vida H., and Almaden, Philip J.: Streptomycin Therapy for Pertussis, J. PEDIAT. 34: 279, 1949.
2. Bell, Joseph A., Pittman, Margaret, and Olson, Byron J.: Pertussis and Aureomycin, Pub. Health Rep. 64: 589, 1949.

News and Notes

The following communication regarding the **Sixth International Pediatric Congress** to be held at Zurich in July, 1950, has been received from Prof. G. Fanconi, president of the Congress:

During the Fifth International Pediatric Congress in New York a Committee of Seven (composed of Professors R. Debré, Paris; Gomez Santos, Mexico; H. F. Helmholz, Rochester, Minn., former president; Emmett Holt, New York, Secretary-General; Maslow, Leningrad; A. Moncrieff, London, and G. Fanconi, Zurich, who was elected President of the Sixth International Pediatric Congress), met in order to draw up rules for the constitution of an international pediatric association (I.P.A.).

Pending the acceptance by the International Congress of 1950, this committee decided the following:

1. To establish a list of the various national Pediatric Societies as well as of their presidents and possibly their members. Dr. Fanconi, as well as Professor E. Holt (Bellevue Hospital, 26th St. and 1st Ave., New York, N. Y.), ask you kindly to send them the required information.
2. To create an international reference journal of pediatrics.
3. To give advice to other organizations concerned with child health and welfare.
4. To organize international regional meetings in order to discuss special problems of immediate importance.

Until the coming Congress in 1950 the official communications of the I.P.A. will be published in six languages in the regular numbers of Helvetica Paediatrica Acta. These will be sent free of charge to the presidents of the national societies.

Dr. Fanconi requests that the various national pediatric societies kindly communicate to him, as soon as possible, suggestions for the main subjects to be discussed at the Sixth International Pediatric Congress.

Book Reviews

The Premature Infant. Julius H. Hess, M.D., and E. C. Lundeen, R.N., Philadelphia, 1949, J. B. Lippincott Company, 381 pages. Price $6.00.

This second edition clearly reflects the increasing medical and public health interest in the premature infant which has been developing in recent years. Dr. Hess, the senior author, has been a pioneer in the field and was responsible for the establishment of the premature infant station in the Michael Reese Hospital in 1922, which led to the "Chicago plan" for city-wide care of the premature infant, and, in turn, to the state plan for Illinois, which has served as a "pilot" for state-wide plans now being established in other commonwealths. Miss Lundeen is the supervisor of the hospital station and has contributed much to the text, as it is genrally recognized that the nursing care of the premature infants is of equal if not greater importance than the medical. Theoretically, it makes an ideal team for a text on the care of the premature infant, and in this instance, the authors have come through with glowing colors. The reader distinctly gets the feeling that the text is based on long and developed personal experience with the premature infant and is not a compilation. The material is presented in a direct and practical manner and the new edition includes the recent developments in chemo- and antibiotic therapy. It can be highly recommended as a practical, thorough, and complete text on the care of the premature infant and his medical and nursing problems.

How to Become a Doctor. George R. Moon, Philadelphia, 1949, The Blakiston Company, 131 pages. Price $2.00.

This book by the Examiner and Recorder of the University of Illinois Colleges of Medicine, Dentistry, and Pharmacy, should be of great help to young men and women who are planning or thinking of becoming a doctor. It is based on an experience of twenty years in which the author has interviewed some 20,000 prospective medical students. The author discusses the quantitative requirements for admission to a medical school and the selection of a college. A detailed but brief summary of the admission requirements to each approved school is then given. The application form is discussed and how it should be completed. The Medical College Admission Test and the way the "Committee on Admissions" functions in a medical school is the theme of the next chapter. There is a brief chapter on success and failure and on the medical course. In subsequent chapters dentistry and pharmacy are discussed.

We know of no other book which covers a similar field, and it should be carefully read by every boy or girl who has a medical career in mind. Throughout the text the author gives sane and sound advice to the prospective medical student based on his years of experience. It should help many young people avoid a lot of disappointment as less than one of three applicants each year can be admitted to the study of medicine.

Poliomyelitis. Papers and Discussions Presented at the First International Poliomyelitis Conference, Philadelphia, 1949, J. B. Lippincott Company, 360 pages. Price $5.00.

This volume contains the papers and discussions presented at the International Poliomyelitis Conference held in New York in July, 1948, which was sponsored by the National Foundation for Infantile Paralysis. A careful reading of the papers and discussions which followed confirms the feeling of those present at the conference that it set a high mark for an international conference. Practically every phase of poliomyelitis and its problems is presented and discussed by authorities in their respective fields. All in all it contains as important a group of essays on poliomyelitis as could have been obtained. Further, the discussions are keen and to the point and have been unusually well edited. There are twenty essays on primary presentation on such subjects as poliomyelitis as a world problem by A. B. Sabin, four on the early stage, such as the pathologic anatomy by David Bodian and treatment by John A. Anderson, four on the convalescent stage, three on bulbar poliomyelitis, three on the problems of immunology and chemotherapy, and three on public health aspects. Each paper was discussed by a number of well-selected workers in the particular field and subject under discussion. The absence of disagreement in the discussions as a whole is quite striking. It is the most valuable discussion of our present-day knowledge of poliomyelitis and its problems which exists and will be of greatest help to all who in one way or another are concerned with or interested in the disease. It is one of the most important contributions that the National Foundation has made, and great credit must go to the general chairman of the conference, Dr. Hart E. Van Riper, for bringing together leading clinical and laboratory authorities from all over the world to share their knowledge. The volume itself, from the printing standpoint, is above average, and obviously much care and thought have been given by the publishers to the format.

Rheumatic Fever: Nursing Care in Pictures. Sabra S. Sadler, R.N., B.S., Philadelphia, 1949, J. B. Lippincott Company, 151 pages.

This is an excellent handbook primarily intended for the public health nurse who has to instruct parents in the daily home care of the patient with rheumatic fever. The various nursing procedures are very simply and completely outlined. In addition, these written instructions are supported by excellent photographs which demonstrate the home nursing techniques.

GOLDRING.

Editor's Column

GASTRIC SUCTION TO PREVENT ASPHYXIA NEONATORUM IN INFANTS DELIVERED BY CESAREAN SECTION

GELLIS, White, and Pfeffer* have introduced the novel procedure of gastric suction to prevent some of the respiratory illness which frequently affects newborn infants of mothers delivered by cesarean section. It is common knowledge that respiratory difficulty is more common after cesarean section than after delivery in the normal way. Respiratory embarrassment which takes place immediately after birth may be accounted for by the use of depressing drugs, anoxic injury to the infant, the aspiration of amniotic fluid, etc. More difficult to explain is the respiratory distress which begins some hours after birth. One mechanism here is the packing of inhaled debris against the alveolar walls. This material at first lies loosely distributed in the alveolar spaces but with each successive inspiration the aspirated debris is pressed against the alveolar walls until a membrane is formed rendering them increasingly impervious.†

The authors present evidence of another mechanism leading to the delayed onset of respiratory difficulties of an obstructive nature with inspiratory retraction, dyspnea, tachypnea, and cyanosis. Suspecting that the aspiration into the lungs of amniotic fluid which had been swallowed at or shortly before birth and then regurgitated might be a factor, they withdrew the gastric contents immediately after delivery. Gastric suction was repeated at three-hour intervals for twelve hours. Ten to 20 c.c. of fluid were usually obtained at the initial aspiration, but in some instances over 30 c.c. were obtained.

Twenty-five infants of diabetic mothers, delivered by cesarean section, were treated in this way. Of these only four showed respiratory symptoms. These were mild and were present at the time of birth. In a control group of infants of diabetic mothers, also delivered by cesarean section but not subjected to gastric suction, six had respiratory difficulties at birth and nine developed symptoms later on. Moreover, the severity of respiratory embarrassment was much greater in the control group. Five infants of diabetic mothers delivered by low forceps had smaller amounts of fluid in the stomach. Only one of these had respiratory difficulty immediately after birth.

In twelve infants of nondiabetic mothers delivered by cesarean section amounts of fluid varying from 6 to 28 c.c. were aspirated from the stomach. Two of the babies had respiratory symptoms at birth. None developed difficulty later on. Fifteen babies of nondiabetic mothers delivered by low forceps had very small amounts of fluid in the stomach.

It appears, then, that babies delivered by cesarean section, whether from diabetic or nondiabetic mothers, frequently have large amounts of fluid in the stomach, in some instances approaching what is generally considered the gastric

*Gellis, S. S., White, P., and Pfeffer, W.: Gastric Suction: A Proposed Additional Technique for the Prevention of Asphyxia in Infants Delivered by Cesarian Section, New England J. Med. 240: 533, 1949.

†Farber, S., and Sweet, L. K.: Amniotic Sac Contents in Lungs of Infants, Am. J. Dis. Child. 42: 1372, 1931.

capacity of the newborn infant (30 to 35 c.c.). This is of interest in relation to the observations of Russ and Strong,* who found increased amounts of material in the tracheas of infants delivered by cesarean section.

In view of the more favorable neonatal course of infants who received gastric suction, Gellis, White, and Pfeffer propose that this procedure be carried out routinely in deliveries by cesarean section, in addition to the measures now commonly employed for the prevention of asphyxia.

AUREOMYCIN AND PERTUSSIS

PERTUSSIS holds about the first place in the group of infectous diseases for which there is no satisfactory therapy. Some evidence has been presented in THE JOURNAL during the last year which indicates that further trials with streptomycin are warranted. Recently Dr. Bell of the Public Health Service and his associates† have shown that aureomycin may have value and needs further study. A similar report was made a week previously by Dr. Bradford of Rochester, N. Y., at a meeting of the American Pediatric Society; it will be published in a subsequent issue of THE JOURNAL.

Bell and his associates found that aureomycin in nontoxic doses delayed or prevented death in mice infected intracerebrally with *Hemophilus pertussis.* Small doses over a period of eight days were more effective than large doses given over a short period of time. Preliminary clinical trials in twenty cases of pertussis apparently shortened the clinical course of the disease. In only a few cases treated early was there a "dramatic response." The authors make no extravagant claims but only that "further clinical trials are necessary to establish its value for general treatment of clinical pertussis." An extensive controlled clinical trial should certainly be made on the basis of these early preliminary reports.

EXCERPTA MEDICA

MANY pediatricians, we find, are unfamiliar with *Excerpta Medica,* an extensive medical abstract service published in Holland by a nonprofit organization and approved by UNESCO. It is in fifteen sections and printed in English. Section VII, Pediatrics, contains about 250 abstracts taken monthly from medical journals published throughout the world. There are about 600 pages, including an index, in the annual volume. Each of the fifteen sections may be subscribed to separately, Section VII costing $15.00 a year. The Williams & Wilkins Company of Baltimore are the agents for the United States. The abstracts are thorough and well written. For the Pediatrics section there are six Americans on the present editorial board of twenty-two. Some 3,500 abstract writers from more than forty countries are cooperating on the fifteen sections. It is far superior to the "Referate" sections of the German pediatric journals upon which we largely depended before the war for an abstract service. *Excerpta Medica* is now in its third year.

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*Russ, J. D., and Strong, R. A.: La Asfixia en el Recien Necido. Bul. Med. del Hosp. Infantil 5: 27, 1948. Idem. Asphyxia of Newborn Infants, Am. J. Obst. & Gynec. 51: 643, 1946.

†Bell, Pittman, and Olson, Pub. Health Rep. 64: 589, May 13, 1949.